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L12        42238 SEA FILE=REGISTRY ABB=ON  PLU=ON  L11 AND C3/ESS
L13             STR

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DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED
ECOUNT  IS M3 C  M1 N  AT   1
ECOUNT  IS M3 C  AT   3

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS   4

STEREO ATTRIBUTES: NONE
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L19          285 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L15(L)(DNA OR RNA OR NUCLEIC
                 ACID OR DEOXYRIBONUC? OR RIBONUC?)
L33            8 SEA FILE=REGISTRY ABB=ON  PLU=ON  DUOCARMYCIN?/CN
L37           21 SEA FILE=HCAPLUS ABB=ON  PLU=ON  ALKYLATION/CT(L)(L33 OR
                 DUOCARMYCIN?) AND L19
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Broad Search for Claim 1

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L37  ANSWER 1 OF 21  HCAPLUS  COPYRIGHT 2003 ACS
ACCESSION NUMBER:         2002:97659  HCAPLUS
DOCUMENT NUMBER:          137:134458
TITLE:                    The DNA phosphate backbone is not involved in
                          catalysis of the duocarmycin and CC-1065 DNA
                          alkylation reaction
AUTHOR(S):                Ambroise, Yves; Boger, Dale L.
CORPORATE SOURCE:         The Scripps Research Institute, Department of
                          Chemistry and The Skaggs Institute for Chemical
                          Biology, La Jolla, CA, 92037, USA
SOURCE:                   Bioorganic & Medicinal Chemistry Letters (2002),
                          12(3), 303-306
                          CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER:                Elsevier Science Ltd.
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
AB   The rates of DNA alkylation were established for the reaction of
     (+)-duocarmycin SA with the native duplex d(G1TCAATTAGTC11).cntdot.d(G12AC
     TAATTGAC22), an 11 bp deoxyoligonucleotide that contains a single
     high-affinity alkylation site that has been structurally characterized at
     exquisite resoln., and modified duplexes in which the four backbone
     phosphates proximal to the C4 carbonyl of bound 1 were replaced with
     methylphosphonates.  All were found to react at comparable rates
     establishing that these backbone phosphates do not participate in
     catalysis of the DNA alkylation reaction.
```

CC 1-3 (Pharmacology)

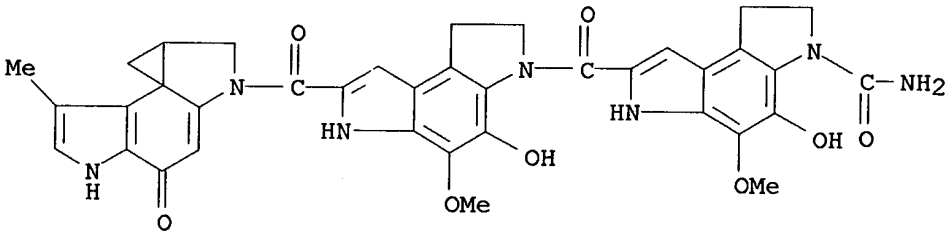
IT **Alkylation**
(DNA; DNA phosphate backbone is not involved in catalysis of **duocarmycin** and CC-1065 DNA alkylation reaction)

IT **69866-21-3,** CC-1065 **118292-34-5,** (+)-Duocarmycin A **130288-24-3,** (+)-Duocarmycin SA
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**DNA** phosphate backbone is not involved in catalysis of duocarmycin and CC-1065 **DNA** alkylation reaction)

IT **69866-21-3,** CC-1065 **118292-34-5,** (+)-Duocarmycin A **130288-24-3,** (+)-Duocarmycin SA
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**DNA** phosphate backbone is not involved in catalysis of duocarmycin and CC-1065 **DNA** alkylation reaction)

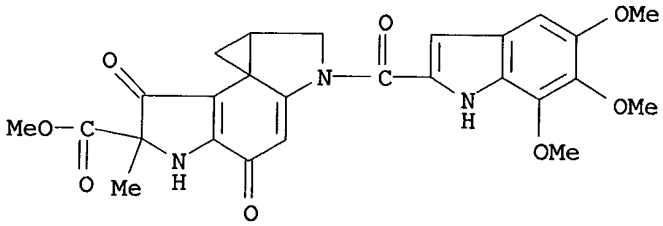
RN 69866-21-3 HCAPLUS

CN Benzo[1,2-b:4,3-b']dipyrrole-3(2H)-carboxamide, 7-[[1,6-dihydro-4-hydroxy-5-methoxy-7-[(4,5,8,8a-tetrahydro-7-methyl-4-oxocyclopropa[c]pyrrolo[3,2-e]indol-2(1H)-yl)carbonyl]benzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-1,6-dihydro-4-hydroxy-5-methoxy-, (7bR,8aS)- (9CI) (CA INDEX NAME)



RN 118292-34-5 HCAPLUS

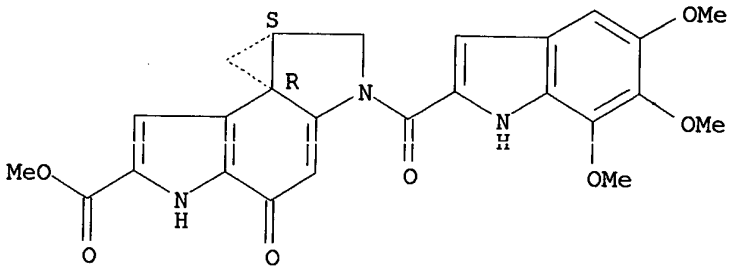
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,6,7,8,8a-octahydro-6-methyl-4,7-dioxo-2-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, methyl ester, (6R,7bR,8aS)- (9CI) (CA INDEX NAME)



RN 130288-24-3 HCAPLUS

CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,8,8a-hexahydro-4-oxo-2-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, methyl ester, (7bR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L37 ANSWER 2 OF 21 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:492794 HCAPLUS
DOCUMENT NUMBER: 133:232444
TITLE: The structural basis for in situ activation of DNA alkylation by duocarmycin SA
AUTHOR(S): Smith, Jarrod A.; Bifulco, Giuseppe; Case, David A.; Boger, Dale L.; Gomez-Paloma, Luigi; Chazin, Walter J.
CORPORATE SOURCE: Department of Molecular Biology, The Scripps Res. Inst., La Jolla, CA, USA
SOURCE: Journal of Molecular Biology (2000), 300(5), 1195-1204
CODEN: JMOBAK; ISSN: 0022-2836
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Duocarmycin SA is a member of a growing class of interesting lead compds. for chemotherapy, distinguished by the manner in which they bind to and react with DNA substrates. The first three-dimensional structure of a DNA adduct of an unnatural enantiomer from this family has been detd. by 1H NMR methods. Comparison to the previously detd. structure of the natural enantiomer bound in the same DNA-binding site provides unique insights into the similarities and crit. distinctions producing the resp. alkylation products and site selectivities. The results also support the hypothesis that the duocarmycin SA alkylation reaction is catalyzed by the binding to DNA, and provide a deeper understanding of the structural basis for this unique mode of activation. (c) 2000 Academic Press.

CC 1-6 (Pharmacology)
Section cross-reference(s): 6

IT **Alkylation**
(biochem.; structural basis for in situ activation of DNA alkylation by **duocarmycin** SA)

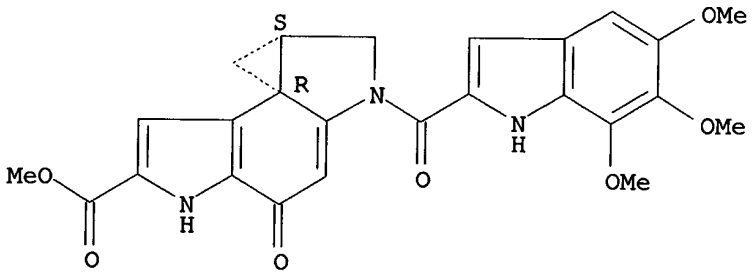
IT **130288-24-3**, Duocarmycin SA
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(structural basis for in situ activation of **DNA** alkylation by duocarmycin SA)

IT **130288-24-3**, Duocarmycin SA
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(structural basis for in situ activation of **DNA** alkylation by duocarmycin SA)

RN 130288-24-3 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,8,8a-

hexahydro-4-oxo-2-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, methyl ester, (7bR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L37 ANSWER 3 OF 21 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:515000 HCAPLUS
DOCUMENT NUMBER: 131:319093
TITLE: Sequence-specific alkylation of DNA by duocarmycin A and its novel derivatives bearing PY/IM polyamides
AUTHOR(S): Tao, Z. -F.; Fujiwara, T.; Saito, I.; Sugiyama, H.
CORPORATE SOURCE: Institute for Medical and Dental Engineering, Tokyo Medical and Dental University, Tokyo, 101-0062, Japan
SOURCE: Nucleosides & Nucleotides (1999), 18(6 & 7), 1615-1616
CODEN: NUNUD5; ISSN: 0732-8311
PUBLISHER: Marcel Dekker, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A new class of sequence-specific DNA alkylating agents was developed based on the reactivity of duocarmycin A and the DNA-reading ability of pyrrole-imidazole polyamide. The DNA alkylation sequence specificity by duocarmycin A can be modulated by a variety of pyrrole-imidazole triamides in a predictable manner. Novel hybrids of the segment A of duocarmycin A and pyrrole-imidazole polyamides efficiently and highly selectively alkylated the target base possessing match sequences of Dervan's binding code.

CC 6-2 (General Biochemistry)

IT **Alkylation**
(biochem.; sequence-specific alkylation of DNA by novel pyrrole-imidazole polyamide derivs. of **duocarmycin** A)

IT **225667-31-2**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(sequence-specific alkylation of **DNA** by novel pyrrole-imidazole polyamide derivs. of duocarmycin A)

IT **118292-34-5**, Duocarmycin A **225667-33-4** **229185-84-6** **248605-35-8**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(sequence-specific alkylation of **DNA** by novel pyrrole-imidazole polyamide derivs. of duocarmycin A)

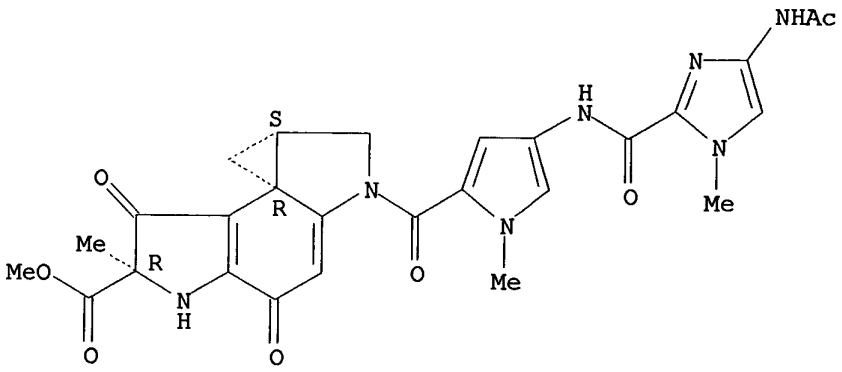
IT **225667-31-2**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL

(Biological study); PROC (Process)
(sequence-specific alkylation of **DNA** by novel pyrrole-imidazole polyamide derivs. of duocarmycin A)

RN 225667-31-2 HCAPLUS

CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 2-[[4-[[[4-(acetylamino)-1-methyl-1H-imidazol-2-yl]carbonyl]amino]-1-methyl-1H-pyrrol-2-yl]carbonyl]-1,2,4,5,6,7,8,8a-octahydro-6-methyl-4,7-dioxo-, methyl ester, (6R,7bR,8aS)- (9CI) (CA INDEX NAME)

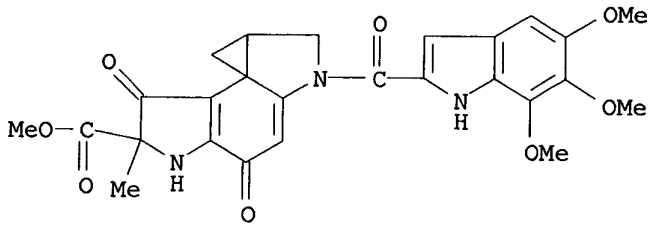
Absolute stereochemistry.



IT **118292-34-5**, Duocarmycin A **225667-33-4**
229185-84-6 248605-35-8
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(sequence-specific alkylation of **DNA** by novel pyrrole-imidazole polyamide derivs. of duocarmycin A)

RN 118292-34-5 HCAPLUS

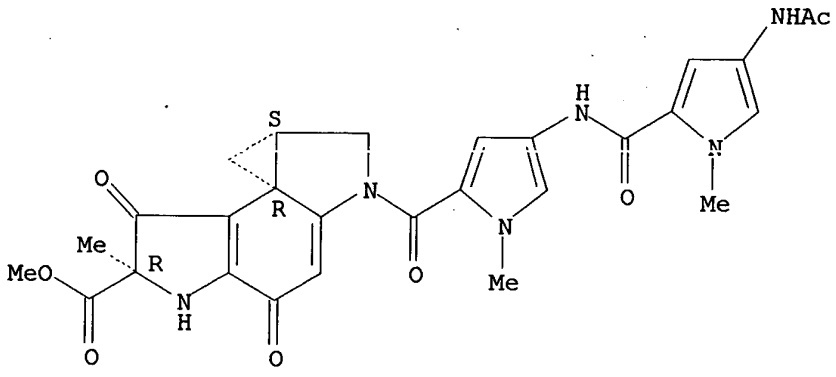
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,6,7,8,8a-octahydro-6-methyl-4,7-dioxo-2-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, methyl ester, (6R,7bR,8aS)- (9CI) (CA INDEX NAME)



RN 225667-33-4 HCAPLUS

CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 2-[[4-[[[4-(acetylamino)-1-methyl-1H-pyrrol-2-yl]carbonyl]amino]-1-methyl-1H-pyrrol-2-yl]carbonyl]-1,2,4,5,6,7,8,8a-octahydro-6-methyl-4,7-dioxo-, methyl ester, (6R,7bR,8aS)- (9CI) (CA INDEX NAME)

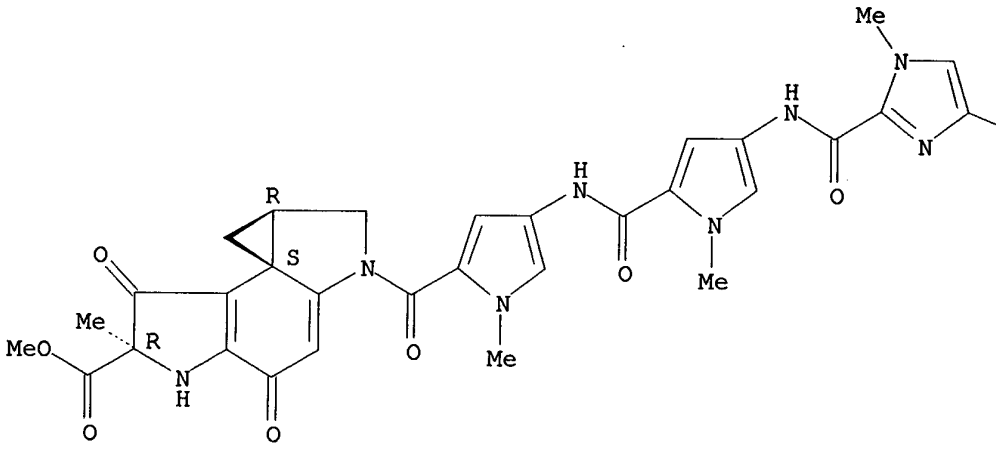
Absolute stereochemistry.



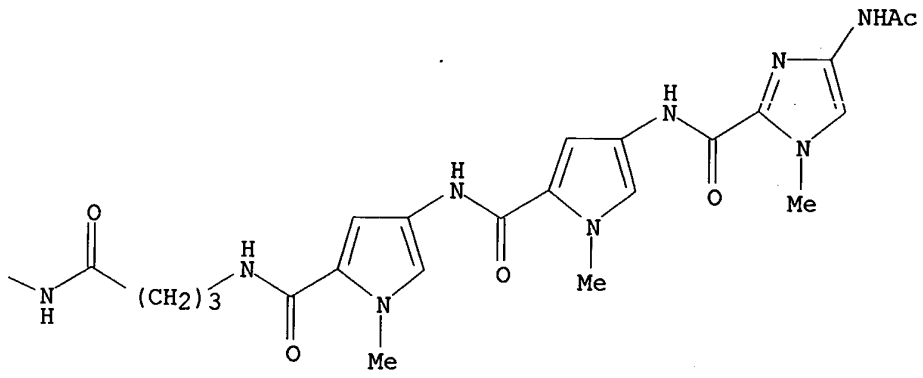
RN 229185-84-6 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 2-[[4-[[[4-[[[4-[[4-[[[4-[[[4-[[[4-(acetylamino)-1-methyl-1H-imidazol-2-yl]carbonyl]amino]-1-methyl-1H-pyrrol-2-yl]carbonyl]amino]-1-methyl-1H-pyrrol-2-yl]carbonyl]amino]-1-oxobutyl]amino]-1-methyl-1H-imidazol-2-yl]carbonyl]amino]-1-methyl-1H-pyrrol-2-yl]carbonyl]amino]-1-methyl-1H-pyrrol-2-yl]carbonyl]-1,2,4,5,6,7,8,8a-octahydro-6-methyl-4,7-dioxo-, methyl ester, (6R,7bS,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



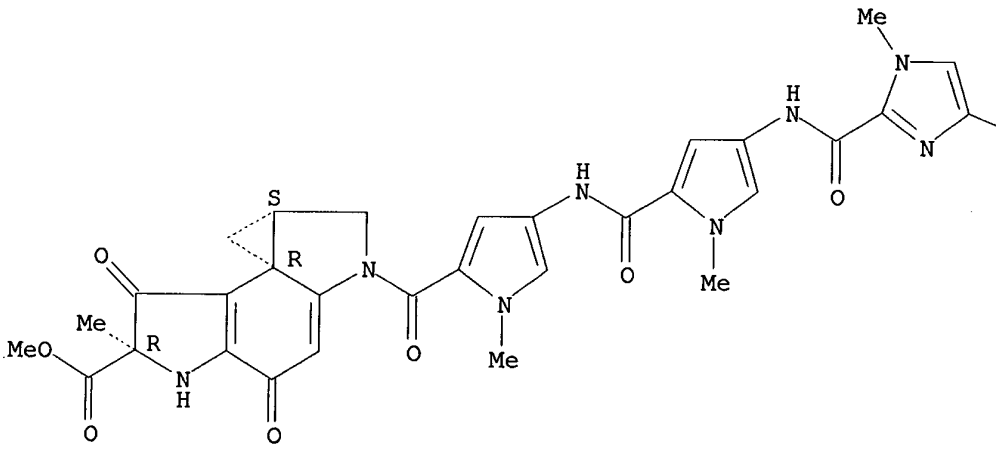
PAGE 1-B



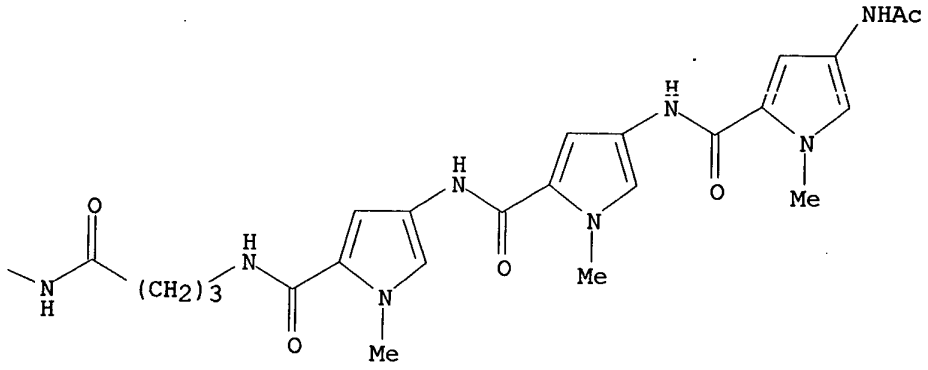
RN 248605-35-8 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 2-[[4-[[[4-[[[4-[[4-[[[4-[[[4-[[[4-(acetylamino)-1-methyl-1H-pyrrol-2-yl]carbonyl]amino]-1-methyl-1H-pyrrol-2-yl]carbonyl]amino]-1-methyl-1H-pyrrol-2-yl]carbonyl]amino]-1-oxobutyl]amino]-1-methyl-1H-imidazol-2-yl]carbonyl]amino]-1-methyl-1H-pyrrol-2-yl]carbonyl]amino]-1-methyl-1H-pyrrol-2-yl]carbonyl]-1,2,4,5,6,7,8,8a-octahydro-6-methyl-4,7-dioxo-, methyl ester, (6R,7bR,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L37 ANSWER 4 OF 21 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:488484 HCAPLUS
DOCUMENT NUMBER: 131:319086
TITLE: Modulation of Sequence Specificity of Duocarmycin-Dependent DNA Alkylation by Pyrrole-Imidazole Triamides
AUTHOR(S): Fujiwara, Tsuyoshi; Tao, Zhi-Fu; Ozeki, Yohei; Saito, Isao; Wang, Andrew H.-J.; Lee, Moses; Sugiyama, Hiroshi
CORPORATE SOURCE: Institute of Biomaterials and Bioengineering, Tokyo Medical and Dental University, Kanda Chiyoda Tokyo, 101-0062, Japan
SOURCE: Journal of the American Chemical Society (1999), 121(33), 7706-7707
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The anticancer antibiotic duocarmycin A (Duo) normally alkylates duplex DNA at the A-N3 site on the 3' side of 3-4 consecutive A-T base pairs. Previous results suggest that the sequence specificity of Duo can be controlled in a predictable manner by pairing with N-methylimidazole/N-methylpyrrole (Py/Im) triamides. The authors synthesized six sets of Im/Py triamides and analyzed the site of DNA alkylation by Duo in the presence of these Im/Py triamides. The results demonstrated that two N-terminal Py or Im residues of the Py/Im triamides minimumly are required in order to define the selectivity of DNA alkylation. Only the Py (or Im) unit of the (Py/Im)-Duo dimer is needed to fulfill the DNA base pair recognition code when the minor groove is filled with an appropriate arom. ligand, such as the B unit of Duo. Py/Im triamides can effectively modulate the site of alkylation by Duo in a predictable manner. These results suggest a promising combinational approach for developing a new type of sequence-specific DNA alkylating agent.

CC 6-2 (General Biochemistry)
Section cross-reference(s): 3

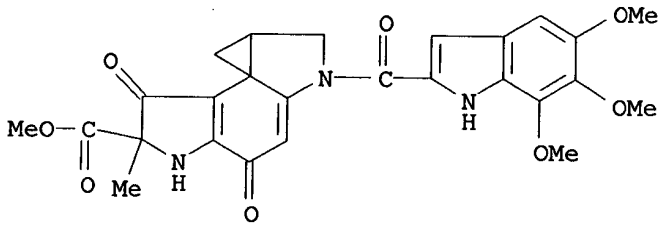
IT Alkylating agents, biological
Alkylation

(modulation of sequence specificity of **duocarmycin**-dependent DNA alkylation by pyrrole-imidazole triamides)

IT **118292-34-5**, Duocarmycin A
RL: BUU (Biological use, unclassified); RCT (Reactant); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(modulation of sequence specificity of duocarmycin-dependent **DNA** alkylation by pyrrole-imidazole triamides)

IT **118292-34-5**, Duocarmycin A
RL: BUU (Biological use, unclassified); RCT (Reactant); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(modulation of sequence specificity of duocarmycin-dependent **DNA** alkylation by pyrrole-imidazole triamides)

RN 118292-34-5 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,6,7,8,8a-octahydro-6-methyl-4,7-dioxo-2-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, methyl ester, (6R,7bR,8aS)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L37 ANSWER 5 OF 21 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:420046 HCAPLUS
DOCUMENT NUMBER: 131:193810
TITLE: Are the Duocarmycin and CC-1065 DNA Alkylation Reactions Acid-Catalyzed? Solvolysis pH-Rate Profiles Suggest They Are Not
AUTHOR(S): Boger, Dale L.; Garbaccio, Robert M.
CORPORATE SOURCE: Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, La Jolla, CA, 92037, USA
SOURCE: Journal of Organic Chemistry (1999), 64(15), 5666-5669
CODEN: JOCEAH; ISSN: 0022-3263
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A study of the solvolysis pH-rate profiles for two key reactive CC-1065/duocarmycin alkylation subunit analogs is detailed. Unlike the authentic alkylation subunits and N-BOC-CBI (4) which are too stable to establish complete solvolysis pH-rate profiles, the analogs N-BOC-CBQ (5) and N-BOC-CNA (6) are reactive throughout the pH range of 2-12. Moreover, they possess progressively diminished vinylogous amide conjugation resulting in a corresponding progressively increasing reactivity adopting and reflecting conformations analogous to that proposed for DNA-bound CC-1065. For both, the acid-catalyzed reaction was obsd. only at the lower pH of 2-5, and the uncatalyzed solvolysis reaction rate dominated at pH .gtoreq.6, indicating that the CC-1065 and duocarmycin DNA alkylation

reaction obsd. at pH 7.4 need not be an acid-catalyzed reaction. The studies provide further strong evidence that catalysis for the DNA alkylation reaction (pH 7.4) is derived from a DNA binding-induced conformational change in the agents that disrupts the stabilizing alkylation subunit vinylogous amide conjugation activating the agents for nucleophilic attack independent of pH.

CC 1-6 (Pharmacology)

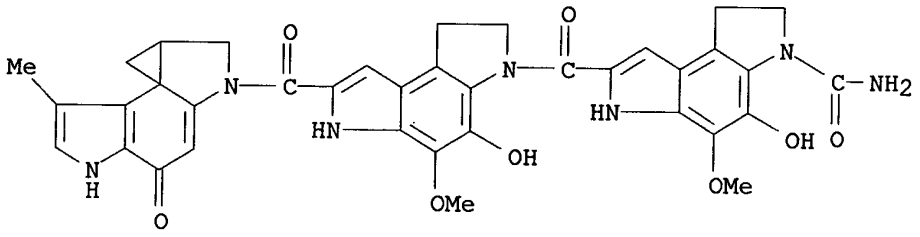
IT **Alkylation**
Antitumor agents
Solvolysis
pH
(**duocarmycin** and CC-1065 DNA alkylation reactions are not acid-catalyzed: solvolysis pH-rate profiles)

IT **69866-21-3,** CC-1065 **118292-34-5,** Duocarmycin A
128300-13-0 **130288-24-3,** Duocarmycin SA
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(duocarmycin and CC-1065 **DNA** alkylation reactions are not acid-catalyzed: solvolysis pH-rate profiles)

IT **69866-21-3,** CC-1065 **118292-34-5,** Duocarmycin A
130288-24-3, Duocarmycin SA
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(duocarmycin and CC-1065 **DNA** alkylation reactions are not acid-catalyzed: solvolysis pH-rate profiles)

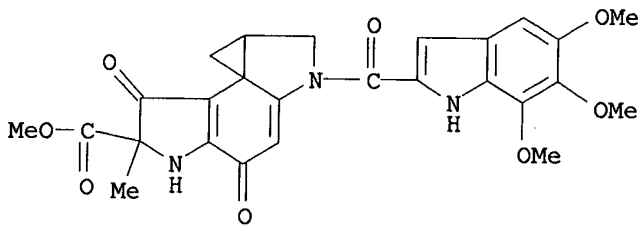
RN 69866-21-3 HCAPLUS

CN Benzo[1,2-b:4,3-b']dipyrrole-3(2H)-carboxamide, 7-[[1,6-dihydro-4-hydroxy-5-methoxy-7-[(4,5,8,8a-tetrahydro-7-methyl-4-oxocyclopropa[c]pyrrolo[3,2-e]indol-2(1H)-yl)carbonyl]benzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-1,6-dihydro-4-hydroxy-5-methoxy-, (7bR,8aS)- (9CI) (CA INDEX NAME)



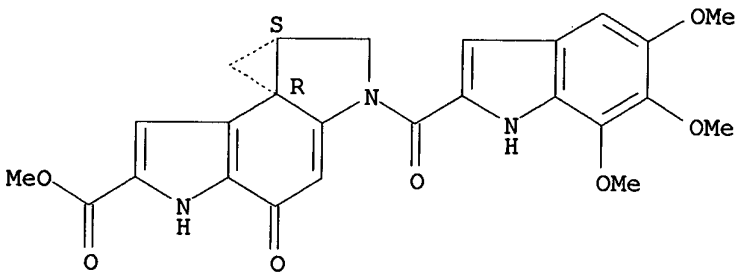
RN 118292-34-5 HCAPLUS

CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,6,7,8,8a-octahydro-6-methyl-4,7-dioxo-2-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, methyl ester, (6R,7bR,8aS)- (9CI) (CA INDEX NAME)



RN 130288-24-3 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,8,8a-hexahydro-4-oxo-2-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, methyl ester, (7bR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L37 ANSWER 6 OF 21 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:701604 HCAPLUS
DOCUMENT NUMBER: 130:75720
TITLE: Critical Role of the Linking Amide in CC-1065 and the Duocarmycins: Implications on the Source of DNA Alkylation Catalysis
AUTHOR(S): Boger, Dale L.; Santillan, Alejandro ,Jr.; Searcey, Mark; Jin, Qing
CORPORATE SOURCE: Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, La Jolla, CA, 92037, USA
SOURCE: Journal of the American Chemical Society (1998), 120(45), 11554-11557
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The prepn. and evaluation of both enantiomers of 5 are described and it constitutes an analog of CBI-TMI (4), the duocarmycins, and CC-1065 in which the amide linking the alkylation and DNA binding subunits has been replaced by a methylene. The agent proved remarkably stable to acid-catalyzed solvolysis consistent with alkylation subunit stabilization derived from a fully engaged vinylogous amide. It was found to exhibit an acid-catalyzed solvolysis half-life (t1/2) of 80 h, 824 h, and .apprx.30,500 h (3.3 days, 34 days, and .apprx.3.5 yr) at pH 1, 2, and 3, resp., and to be completely stable at pH 7. The removal of the linking amide resulted in a 105-fold loss in cytotoxic potency and the complete loss of DNA alkylation capabilities providing an agent that is >106.times. less effective than 4 and >102.times. less effective than even N-BOC-CBI or N-Ac-CBI. These observations highlight the crit. importance of the linking amide and implicate a fundamental role in DNA alkylation catalysis. Thus, rather than enhancing DNA alkylation by facilitating C4 carbonyl protonation (acid catalysis), the removal of the linking amide abolished the capabilities for DNA alkylation. This is consistent with the intimate participation of the linking amide in catalysis derived from

a DNA binding-induced conformation change that serves to disrupt the alkylation subunit cross-conjugated vinylogous amide stabilization activating the agents for nucleophilic attack.

CC 1-3 (Pharmacology)
Section cross-reference(s): 26

IT **Alkylation**
Cytotoxicity
Structure-activity relationship
(role of linking amide in the antitumor antibiotics CC-1065 and **duocarmycins** and implications on source of DNA alkylation catalysis studied by prepg. structural analogs without the linking amide)

IT 218922-34-0P **218922-36-2P**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); PROC (Process)
(role of linking amide in the antitumor antibiotics CC-1065 and duocarmycins and implications on source of **DNA** alkylation catalysis studied by prepg. structural analogs without the linking amide)

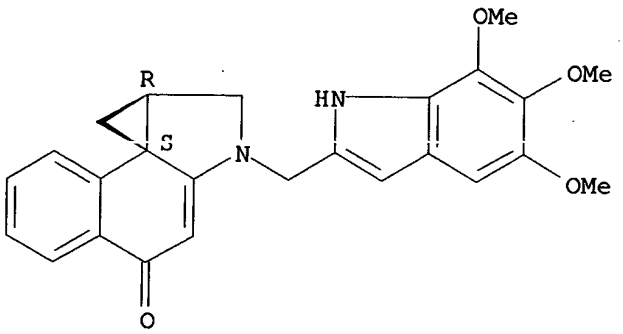
IT **218922-06-6P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); PROC (Process)
(role of linking amide in the antitumor antibiotics CC-1065 and duocarmycins and implications on source of **DNA** alkylation catalysis studied by prepg. structural analogs without the linking amide)

IT **69866-21-3**, CC-1065 **118292-34-5**, (+)-Duocarmycin A
130288-24-3, (+)-Duocarmycin SA **157922-78-6**, (+)-CBI-TMI
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(role of linking amide in the antitumor antibiotics CC-1065 and duocarmycins and implications on source of **DNA** alkylation catalysis studied by prepg. structural analogs without the linking amide)

IT **218922-36-2P**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); PROC (Process)
(role of linking amide in the antitumor antibiotics CC-1065 and duocarmycins and implications on source of **DNA** alkylation catalysis studied by prepg. structural analogs without the linking amide)

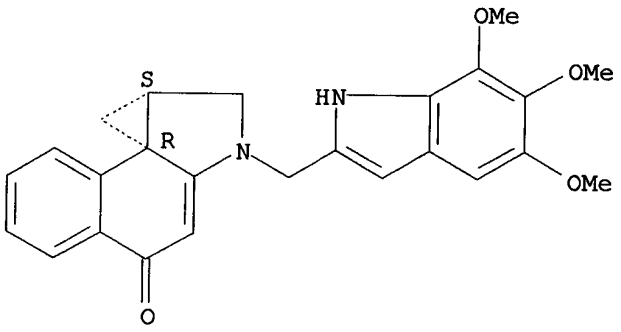
RN 218922-36-2 HCAPLUS
CN 4H-Benzo[e]cycloprop[c]indol-4-one, 1,2,9,9a-tetrahydro-2-[(5,6,7-trimethoxy-1H-indol-2-yl)methyl]-, (8bS,9aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

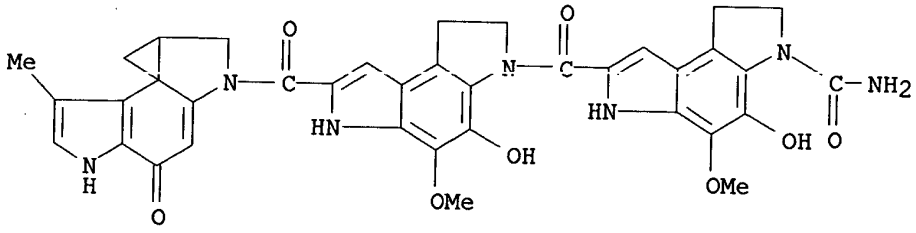


IT **218922-06-6P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); PROC (Process)
(role of linking amide in the antitumor antibiotics CC-1065 and duocarmycins and implications on source of **DNA** alkylation catalysis studied by prepg. structural analogs without the linking amide)
RN 218922-06-6 HCAPLUS
CN 4H-Benzo[e]cycloprop[c]indol-4-one, 1,2,9,9a-tetrahydro-2-[(5,6,7-trimethoxy-1H-indol-2-yl)methyl]-, (8bR,9aS)- (9CI) (CA INDEX NAME)

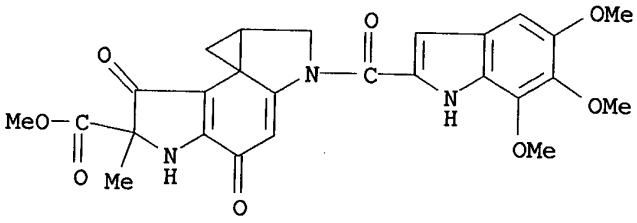
Absolute stereochemistry. Rotation (+).



IT **69866-21-3**, CC-1065 **118292-34-5**, (+)-Duocarmycin A
130288-24-3, (+)-Duocarmycin SA **157922-78-6**, (+)-CBI-TMI
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(role of linking amide in the antitumor antibiotics CC-1065 and duocarmycins and implications on source of **DNA** alkylation catalysis studied by prepg. structural analogs without the linking amide)
RN 69866-21-3 HCAPLUS
CN Benzo[1,2-b:4,3-b']dipyrrole-3(2H)-carboxamide, 7-[[1,6-dihydro-4-hydroxy-5-methoxy-7-[(4,5,8,8a-tetrahydro-7-methyl-4-oxocyclopropa[c]pyrrolo[3,2-e]indol-2(1H)-yl)carbonyl]benzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-1,6-dihydro-4-hydroxy-5-methoxy-, (7bR,8aS)- (9CI) (CA INDEX NAME)

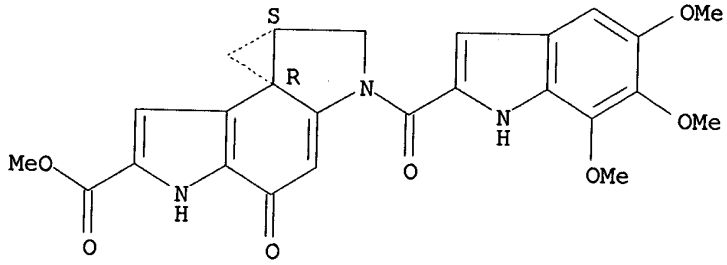


RN 118292-34-5 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,6,7,8,8a-octahydro-6-methyl-4,7-dioxo-2-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, methyl ester, (6R,7bR,8aS)- (9CI) (CA INDEX NAME)



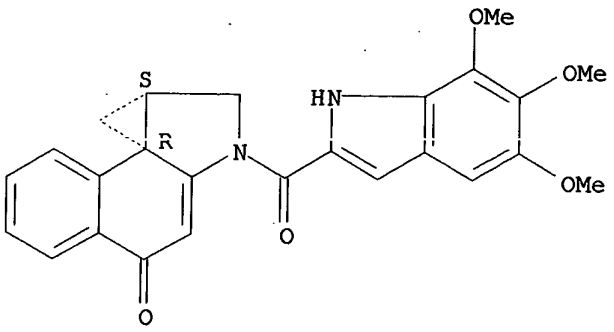
RN 130288-24-3 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,8,8a-hexahydro-4-oxo-2-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, methyl ester, (7bR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 157922-78-6 HCAPLUS
CN 4H-Benzo[e]cycloprop[c]indol-4-one, 1,2,9,9a-tetrahydro-2-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, (8bR,9aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 56 THERE ARE 56 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L37 ANSWER 7 OF 21 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:589817 HCAPLUS
DOCUMENT NUMBER: 129:299322
TITLE: Sequence selective DNA alkylation by duocarmycin derivatives using molecular recognition of pyrrole-imidazole polyamide
AUTHOR(S): Fujiwara, Tsuyoshi; Tao, Zhi-Fu; Ozeki, Youhei; Saito, Isao; Sugiyama, Hiroshi
CORPORATE SOURCE: Institute for Medical and Dental Engineering, Tokyo Medical and Dental University, Tokyo, 101-0062, Japan
SOURCE: Nucleic Acids Symposium Series (1998), 39, 101-102
CODEN: NACSD8; ISSN: 0261-3166
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Duocarmycin A (Duo) itself alkylates adenine N3 at the 3' end A+T-rich sequences in DNA. Recently, we described that the addn. of another minor groove binder, distamycin A (Dist), dramatically modulates the site of DNA alkylation by Duo and revealed a highly efficient G-N3 alkylation via the cooperative binding of a heterodimer between Duo and Dist in the DNA minor groove. Herein we describe new ways to alter the DNA alkylation selectivity in a predictive manner using two different methods. One way is the addn. of other minor groove binder, pyrrole (Py)-imidazole (Im) triamides, instead of Dist. Another way is the synthesis of novel conjugates of Duo segment A and Py-Im oligoamides. Both approaches were revealed to efficiently modulate the site of alkylation by Duo in a predicted manner.

CC 6-2 (General Biochemistry)

IT **Alkylation**
(biochem.; sequence selective DNA alkylation by **duocarmycin** derivs. using mol. recognition of pyrrole-imidazole polyamide)

IT **214558-41-5**
RL: BPR (Biological process); BSU (Biological study, unclassified); RCT (Reactant); BIOL (Biological study); PROC (Process); RACT (Reactant or reagent)
(sequence seblective **DNA** alkylation by duocarmycin derivs. using mol. recognition of pyrrole-imidazole polyamide)

IT 636-47-5, Distamycin A **214558-42-6 214558-43-7 214558-44-8 214558-45-9 214558-46-0 214558-47-1**

RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)
(sequence selective **DNA** alkylation by duocarmycin derivs. using mol. recognition of pyrrole-imidazole polyamide)

IT **118292-34-5**, Duocarmycin A **153925-97-4**, Du86
RL: BPR (Biological process); BSU (Biological study, unclassified); RCT (Reactant); BIOL (Biological study); PROC (Process); RACT (Reactant or reagent)
(sequence selective **DNA** alkylation by duocarmycin derivs. using mol. recognition of pyrrole-imidazole polyamide)

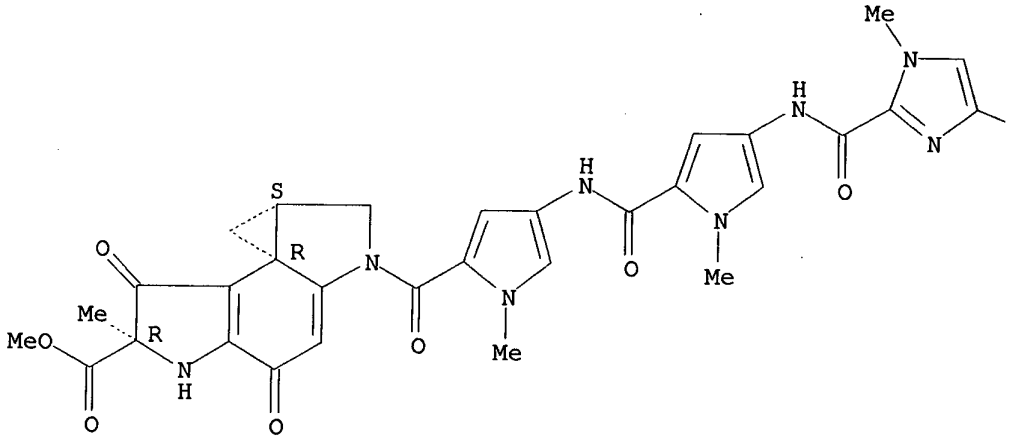
IT **214558-41-5**
RL: BPR (Biological process); BSU (Biological study, unclassified); RCT (Reactant); BIOL (Biological study); PROC (Process); RACT (Reactant or reagent)
(sequence seblective **DNA** alkylation by duocarmycin derivs. using mol. recognition of pyrrole-imidazole polyamide)

RN 214558-41-5 HCAPLUS

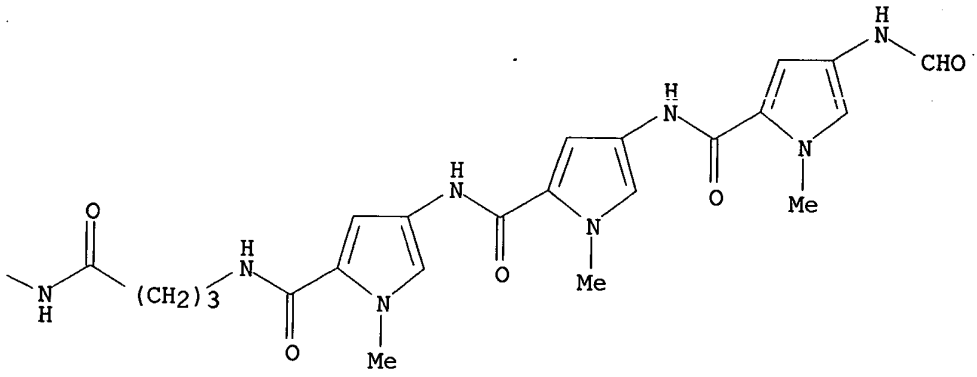
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 2-[[4-[[[4-[[[4-[[4-[[[4-[[[4-[[[4-(formylamino)-1-methyl-1H-pyrrol-2-yl]carbonyl]amino]-1-methyl-1H-pyrrol-2-yl]carbonyl]amino]-1-methyl-1H-pyrrol-2-yl]carbonyl]amino]-1-oxobutyl]amino]-1-methyl-1H-imidazol-2-yl]carbonyl]amino]-1-methyl-1H-pyrrol-2-yl]carbonyl]amino]-1-methyl-1H-pyrrol-2-yl]carbonyl]-1,2,4,5,6,7,8,8a-octahydro-6-methyl-4,7-dioxo-, methyl ester, (6R,7bR,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

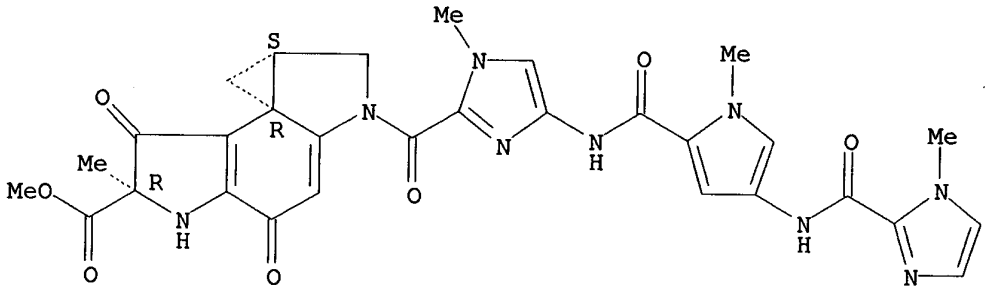


IT **214558-42-6 214558-43-7 214558-44-8**
214558-45-9 214558-46-0 214558-47-1
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)
(sequence selective **DNA** alkylation by duocarmycin derivs. using mol. recognition of pyrrole-imidazole polyamide)

RN 214558-42-6 HCAPLUS

CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,6,7,8,8a-octahydro-6-methyl-2-[[1-methyl-4-[[[1-methyl-4-[[(1-methyl-1H-imidazol-2-yl)carbonyl]amino]-1H-pyrrol-2-yl]carbonyl]amino]-1H-imidazol-2-yl]carbonyl]-4,7-dioxo-, methyl ester, (6R,7bR,8aS)- (9CI) (CA INDEX NAME)

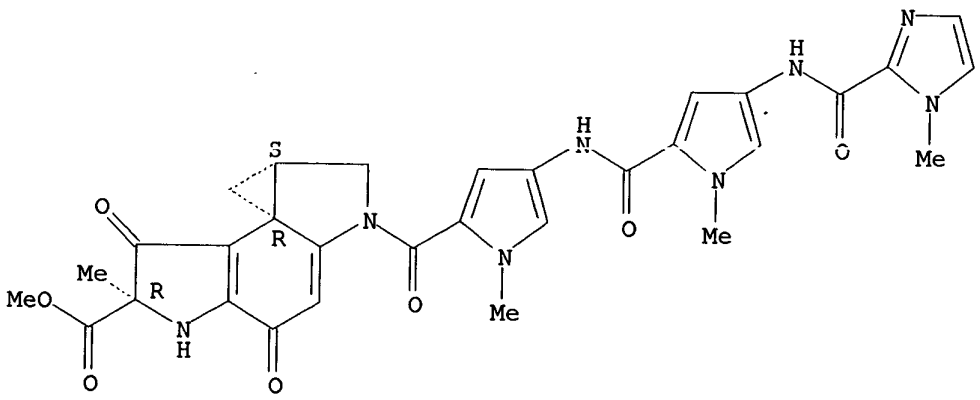
Absolute stereochemistry.



RN 214558-43-7 HCAPLUS

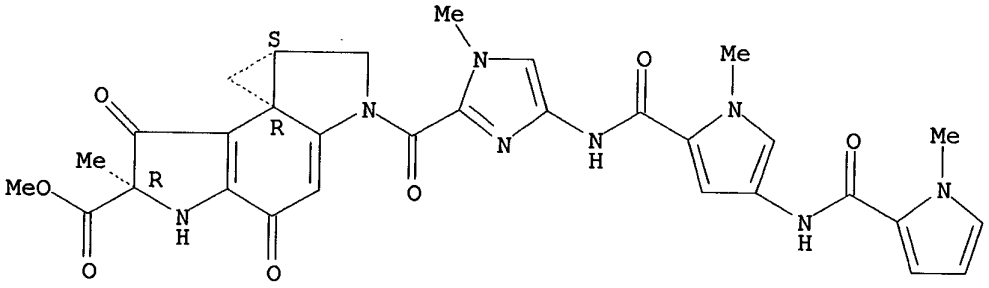
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,6,7,8,8a-octahydro-6-methyl-2-[[1-methyl-4-[[[1-methyl-4-[[(1-methyl-1H-imidazol-2-yl)carbonyl]amino]-1H-pyrrol-2-yl]carbonyl]amino]-1H-pyrrol-2-yl]carbonyl]-4,7-dioxo-, methyl ester, (6R,7bR,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



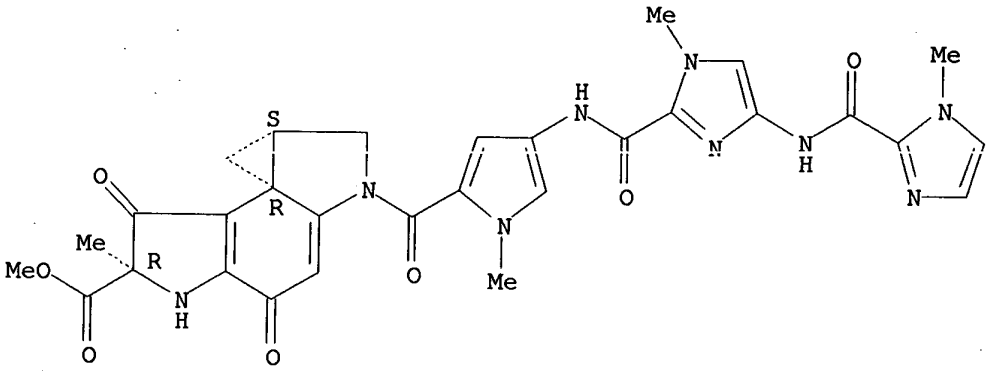
RN 214558-44-8 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,6,7,8,8a-octahydro-6-methyl-2-[[1-methyl-4-[[[1-methyl-4-[[(1-methyl-1H-pyrrol-2-yl)carbonyl]amino]-1H-pyrrol-2-yl]carbonyl]amino]-1H-imidazol-2-yl]carbonyl]-4,7-dioxo-, methyl ester, (6R,7bR,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



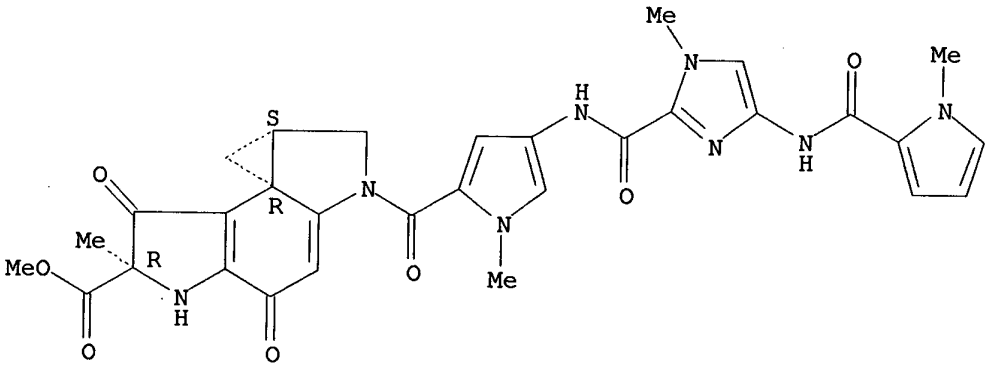
RN 214558-45-9 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,6,7,8,8a-octahydro-6-methyl-2-[[1-methyl-4-[[[1-methyl-4-[[(1-methyl-1H-imidazol-2-yl)carbonyl]amino]-1H-imidazol-2-yl]carbonyl]amino]-1H-pyrrol-2-yl]carbonyl]-4,7-dioxo-, methyl ester, (6R,7bR,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 214558-46-0 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,6,7,8,8a-octahydro-6-methyl-2-[[1-methyl-4-[[[1-methyl-4-[[(1-methyl-1H-pyrrol-2-yl)carbonyl]amino]-1H-imidazol-2-yl]carbonyl]amino]-1H-pyrrol-2-yl]carbonyl]-4,7-dioxo-, methyl ester, (6R,7bR,8aS)- (9CI) (CA INDEX NAME)

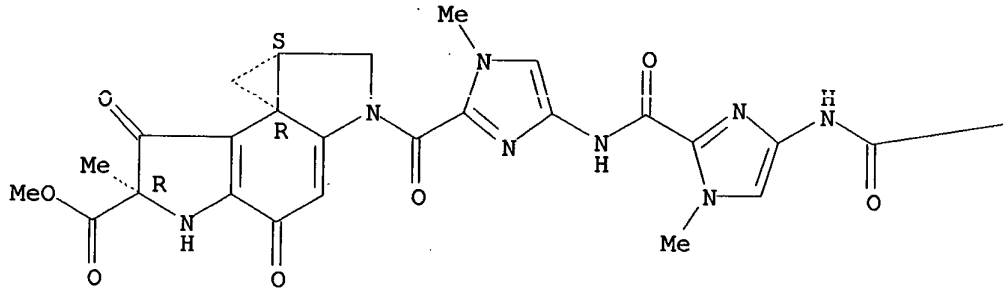
Absolute stereochemistry.



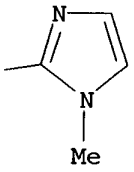
RN 214558-47-1 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,6,7,8,8a-octahydro-6-methyl-2-[[1-methyl-4-[[[1-methyl-4-[[(1-methyl-1H-imidazol-2-yl)carbonyl]amino]-1H-imidazol-2-yl]carbonyl]amino]-1H-imidazol-2-yl]carbonyl]-4,7-dioxo-, methyl ester, (6R,7bR,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



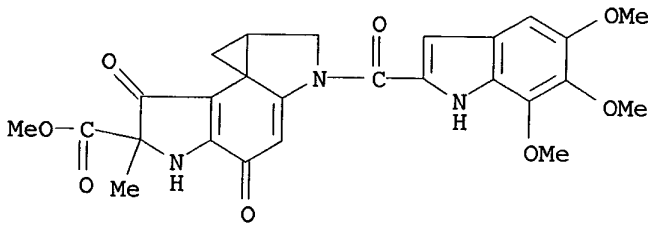
PAGE 1-B



TT **118292-34-5**, Duocarmycin A **153925-97-4**, Du86
RL: BPR (Biological process); BSU (Biological study, unclassified); RCT (Reactant); BIOL (Biological study); PROC (Process); RACT (Reactant or reagent)
(sequence selective **DNA** alkylation by duocarmycin derivs. using mol. recognition of pyrrole-imidazole polyamide)

RN 118292-34-5 HCAPLUS

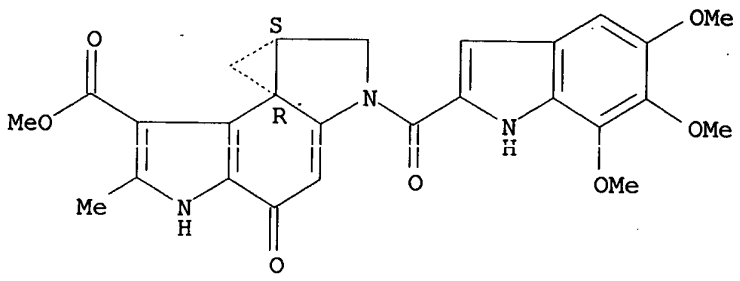
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,6,7,8,8a-octahydro-6-methyl-4,7-dioxo-2-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, methyl ester, (6R,7bR,8aS)- (9CI) (CA INDEX NAME)



RN 153925-97-4 HCAPLUS

CN Cyclopropa[c]pyrrolo[3,2-e]indole-7-carboxylic acid, 1,2,4,5,8,8a-hexahydro-6-methyl-4-oxo-2-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, methyl ester, (7bR,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L37 ANSWER 8 OF 21 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:294293 HCAPLUS
DOCUMENT NUMBER: 129:27839
TITLE: Cooperative alkylation by duocarmycin A-distamycin A heterodimer
AUTHOR(S): Ozeki, Youhei; Sugiyama, Hiroshi; Saito, Isao
CORPORATE SOURCE: Dep. of Synthetic Chemistry and Biological Chemistry, Faculty of Engineering, Kyoto University, Kyoto, 606-01, Japan
SOURCE: Nucleic Acids Symposium Series (1997), 37(Symposium on Nucleic Acids Chemistry, 1997), 91-92
CODEN: NACSD8; ISSN: 0261-3166
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Duocarmycin A (Duo) normally alkylates adenine N-3 at the 3' end of A+T-rich sequences in DNA. The addn. of an other minor groove binder, distamycin A (Dist), dramatically modulate the site of DNA alkylation by Duo with great acceleration of the reaction rate. In order to examine the mode of alkylation, the kinetics of the reaction under various conditions were examd. Based on the simulation of exptl. data, a new reaction path was proposed. A ternary complex of Duo and Dist with DNA was obsd.

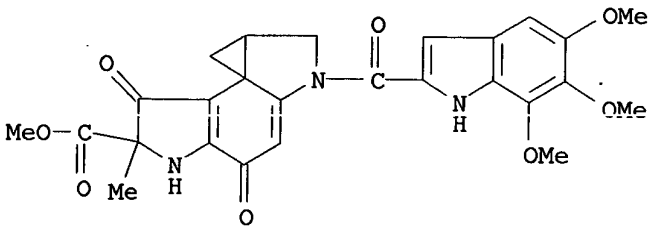
CC 26-6 (Biomolecules and Their Synthetic Analogs)
Section cross-reference(s): 6, 33

IT **Alkylation**
Alkylation kinetics
(alkylation of DNA by **duocarmycin** A and distamycin A)

IT 636-47-5, Distamycin A **118292-34-5**, Duocarmycin A
RL: BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); RCT (Reactant); BIOL (Biological study); PROC (Process); RACT (Reactant or reagent)
(alkylation of **DNA** by duocarmycin A and distamycin A)

IT **118292-34-5**, Duocarmycin A
RL: BSU (Biological study, unclassified); PEP (Physical, engineering or chemical process); RCT (Reactant); BIOL (Biological study); PROC (Process); RACT (Reactant or reagent)
(alkylation of **DNA** by duocarmycin A and distamycin A)

RN 118292-34-5 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,6,7,8,8a-octahydro-6-methyl-4,7-dioxo-2-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, methyl ester, (6R,7bR,8aS)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L37 ANSWER 9 OF 21 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:786546 HCAPLUS
DOCUMENT NUMBER: 128:3563
TITLE: Synthesis and Evaluation of CC-1065 and Duocarmycin Analogs Incorporating the Iso-CI and Iso-CBI Alkylation Subunits: Impact of Relocation of the C-4 Carbonyl
AUTHOR(S): Boger, Dale L.; Garbaccio, Robert M.; Jin, Qing
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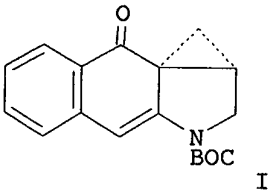
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



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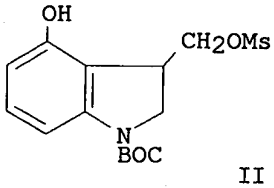

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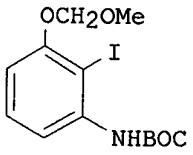

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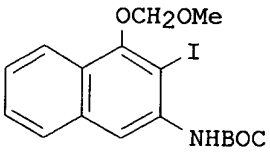


IV

AB The synthesis of 2-(tert-Butyloxycarbonyl)-1,2,9,9a-tetrahydrocyclopropa[c]benzo[f]indol-8-one [I (N-BOC-iso-CBI)] and 1-(tert-Butyloxycarbonyl)-4-hydroxy-3-[[(methanesulfonyl)oxy]methyl]-2,3-dihydroindole [II; Ms = SO2Me (seco-N-BOC-iso-CI)] contg. an isomeric structural modification in the CC-1065 and duocarmycin alkylation subunits and their incorporation into analogs of the natural products are detailed. The approach was based on a directed ortho metalation of an appropriately

functionalized benzene, e.g. III, or naphthalene, e.g. IV, precursor to regiospecifically install iodine at the C-2 position. Conversion of these resp. intermediates to the dihydroindole skeleton utilized an established 5-exo-trig aryl radical cyclization onto an unactivated alkene with subsequent TEMPO trap or the more recent 5-exo-trig aryl radical cyclization onto a vinyl chloride for direct synthesis of the immediate precursors. Closure of the activated cyclopropane to complete the iso-CBI nucleus was accomplished by a selective ortho spirocyclization. The evaluation of the iso-CBI-based agents revealed a significant stability comparable to that of CC-1065 and duocarmycin A, but that it is more reactive than duocarmycin SA (6-7.times.) or the direct comparison CBI-based agents (5.times.) for which X-ray structure comparisons served to establish the basis for their inherent reaction regioselectivity and reactivity. Resoln. and synthesis of a full set of natural product analogs and subsequent evaluation of their DNA alkylation properties revealed that the iso-CBI analogs, even with the relocation of the C-4 carbonyl and the most substantial structural modifications to the alkylation subunit to date, reacted at comparable rates and retain the identical and characteristic sequence selectivity of CC-1065 and the duocarmycins. This observation is inconsistent with the proposal that a sequence-dependent C-4 carbonyl protonation by strategically located DNA backbone phosphates controls the DNA alkylation selectivity but is consistent with the proposal that it is detd. by the AT-rich noncovalent binding selectivity of the agents and the steric accessibility of the N3 alkylation site. Confirmation that the DNA alkylation reaction is derived from adenine N3 addn. to the least substituted carbon of the activated cyclopropane, and its quantitation (95%) was established by isolation and characterization of the depurination adenine N3 adduct. Consistent with past studies and despite the deep-seated structural change in the alkylation subunit, the agents were found to exhibit potent cytotoxic activity that correlates with their inherent reactivity.

CC 26-6 (Biomolecules and Their Synthetic Analogs)
Section cross-reference(s): 75

IT **Alkylation**
Crystal structure
Cytotoxicity
QSAR (structure-activity relationship)
(synthesis and evaluation of CC-1065 and **duocarmycin** analogs in DNA alkylation)

IT **101222-80-4 110352-07-3,** (-)-CC-1065 **114251-19-3**
114977-72-9 119904-99-3 **127232-82-0**
127306-33-6 127379-15-1 **128049-56-9**
128049-57-0 128050-92-0 128050-93-1
128300-13-0 **128300-14-1 128300-15-2**
128300-16-3 128300-17-4 128571-50-6, (+)-CBI
130007-87-3 130007-90-8, (-)-CBI 132746-32-8 133696-93-2
135306-52-4 141781-45-5 144224-62-4
144732-53-6 **149251-66-1 149405-55-0,** (-)-Duocarmycin A
149405-58-3, (+)-epi-Duocarmycin A **149405-59-4**
150992-82-8, (+)-DSA 151062-83-8, (-)-DSA **151062-84-9,**
(-)-Duocarmycin SA 151062-86-1 157035-50-2 157035-51-3
157922-78-6 157968-94-0 160542-95-0
160637-26-3 161442-84-8 **161442-89-3**
161442-90-6 173655-21-5 173655-22-6 173655-23-7
173655-24-8, (-)-MCBI **173655-25-9 173655-26-0**
173655-27-1 173655-28-2 173655-29-3
173655-30-6 173655-31-7 173655-32-8

176442-53-8 178962-97-5 **178962-98-6 178962-99-7**
178963-00-3 178963-01-4 178963-02-5
178963-03-6 178963-04-7 178963-05-8, (-)-CCBI 181574-83-4
181574-87-8 186355-63-5 186356-12-7 186356-13-8
190060-29-8 190060-30-1 190060-45-8
190060-46-9 194221-81-3 194222-28-1 **194222-35-0**
194222-36-1 194222-38-3 194222-46-3
198710-00-8 198710-03-1 198710-05-3
198710-10-0, (.+-.)-CBQ
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(synthesis and evaluation of CC-1065 and duocarmycin analogs in **DNA** alkylation)

IT **69866-21-3DP**, (+)-CC-1065, analogs **118292-34-5DP**, (+)-Duocarmycin A, analogs **130288-24-3DP**, (+)-Duocarmycin SA, analogs 198709-06-7P 198709-08-9P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(synthesis and evaluation of CC-1065 and duocarmycin analogs in **DNA** alkylation)

IT 198709-32-9P **198709-35-2P 198709-37-4P** 198709-42-1P
198709-46-5P 198709-50-1P 198709-54-5P
198709-58-9P 198709-62-5P 198709-66-9P
198709-72-7P 198709-75-0P 198709-79-4P
198709-83-0P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(synthesis and evaluation of CC-1065 and duocarmycin analogs in **DNA** alkylation)

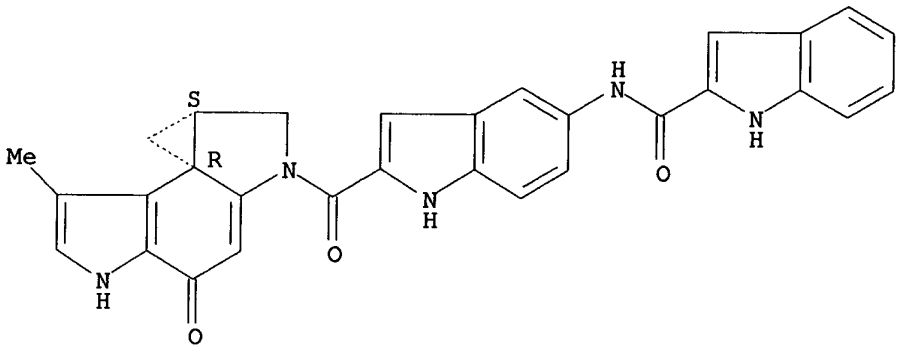
IT 198708-93-9P 198708-94-0P **198709-10-3P 198709-12-5P**
198709-14-7P 198709-16-9P 198709-18-1P
198709-20-5P 198709-25-0P 198709-34-1P 198709-44-3P
RL: SPN (Synthetic preparation); PREP (Preparation)
(synthesis and evaluation of CC-1065 and duocarmycin analogs in **DNA** alkylation)

IT **101222-80-4 110352-07-3**, (-)-CC-1065 **114251-19-3**
114977-72-9 127232-82-0 127306-33-6
128049-56-9 128049-57-0 128050-92-0
128050-93-1 128300-14-1 128300-15-2
128300-16-3 128300-17-4 135306-52-4
141781-45-5 144224-62-4 149251-66-1
149405-55-0, (-)-Duocarmycin A **149405-58-3**,
(+)-epi-Duocarmycin A **149405-59-4 151062-84-9**,
(-)-Duocarmycin SA **157922-78-6 157968-94-0**
160542-95-0 160637-26-3 161442-89-3
161442-90-6 173655-25-9 173655-26-0
173655-27-1 173655-28-2 173655-29-3
173655-30-6 173655-31-7 173655-32-8
178962-98-6 178962-99-7 178963-00-3
178963-01-4 178963-02-5 178963-03-6
181574-87-8 190060-29-8 190060-30-1
190060-45-8 190060-46-9 194222-35-0
194222-36-1 194222-38-3 194222-46-3
198710-00-8 198710-03-1 198710-05-3
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

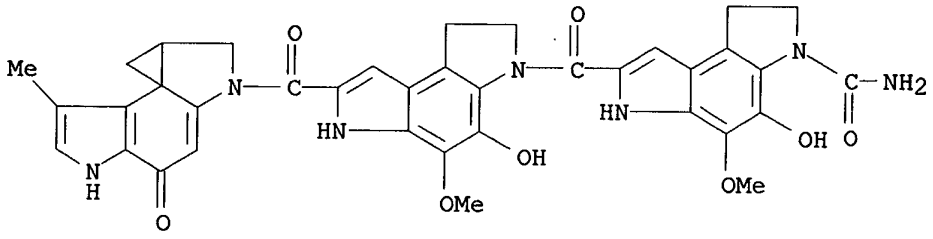
study, unclassified); BIOL (Biological study)
(synthesis and evaluation of CC-1065 and duocarmycin analogs in **DNA** alkylation)

RN 101222-80-4 HCAPLUS
CN 1H-Indole-2-carboxamide, N-[2-[[(7bR,8aS)-4,5,8,8a-tetrahydro-7-methyl-4-oxocyclopropa[c]pyrrolo[3,2-e]indol-2(1H)-yl]carbonyl]-1H-indol-5-yl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



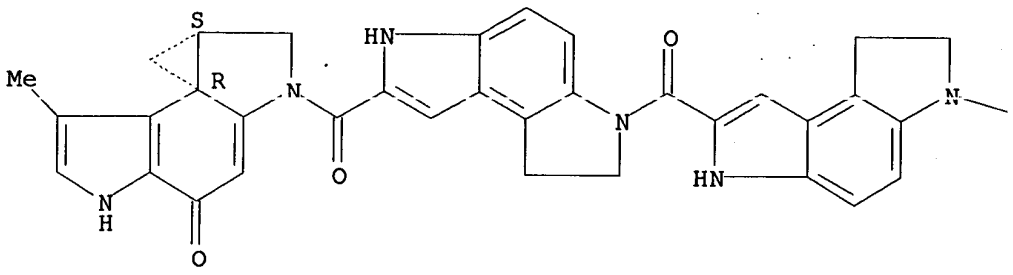
RN 110352-07-3 HCAPLUS
CN Benzo[1,2-b:4,3-b']dipyrrole-3(2H)-carboxamide, 7-[[1,6-dihydro-4-hydroxy-5-methoxy-7-[[(7bS,8aR)-4,5,8,8a-tetrahydro-7-methyl-4-oxocyclopropa[c]pyrrolo[3,2-e]indol-2(1H)-yl]carbonyl]benzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-1,6-dihydro-4-hydroxy-5-methoxy- (9CI) (CA INDEX NAME)



RN 114251-19-3 HCAPLUS
CN Benzo[1,2-b:4,3-b']dipyrrole-3(2H)-carboxamide, 7-[[1,6-dihydro-7-[(4,5,8,8a-tetrahydro-7-methyl-4-oxocyclopropa[c]pyrrolo[3,2-e]indol-2(1H)-yl)carbonyl]benzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-1,6-dihydro-, (7bR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

PAGE 1-A



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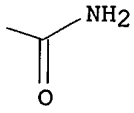
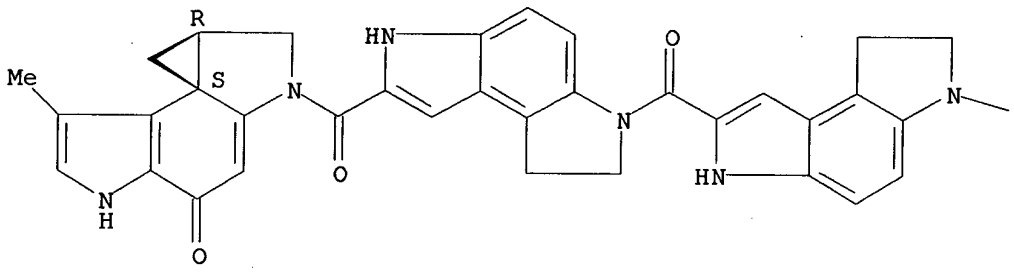


RN 114977-72-9 HCAPLUS
CN Benzo[1,2-b:4,3-b']dipyrrole-3(2H)-carboxamide, 7-[[1,6-dihydro-7-[[4,5,8,8a-tetrahydro-7-methyl-4-oxocyclopropa[c]pyrrolo[3,2-e]indol-2(1H)-yl]carbonyl]benzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-1,6-dihydro-, (8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

PAGE 1-A



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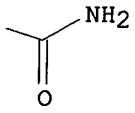
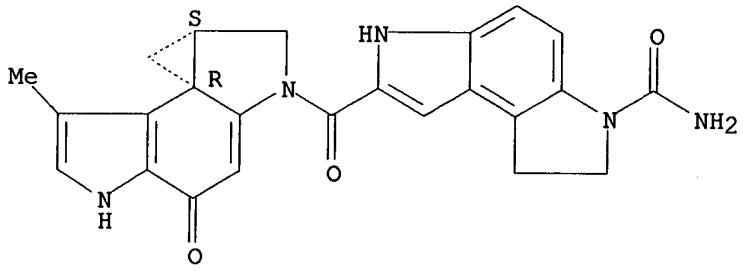


RN 127232-82-0 HCAPLUS

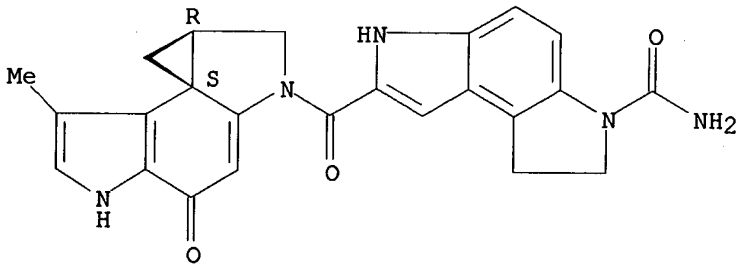
CN Benzo[1,2-b:4,3-b']dipyrrole-3(2H)-carboxamide, 1,6-dihydro-7-[(4,5,8,8a-tetrahydro-7-methyl-4-oxocyclopropa[c]pyrrolo[3,2-e]indol-2(1H)-yl)carbonyl]-, (7bR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 127306-33-6 HCAPLUS
CN Benzo[1,2-b:4,3-b']dipyrrole-3(2H)-carboxamide, 1,6-dihydro-7-[(4,5,8,8a-tetrahydro-7-methyl-4-oxocyclopropa[c]pyrrolo[3,2-e]indol-2(1H)-yl)carbonyl]-, (7bS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 128049-56-9 HCAPLUS
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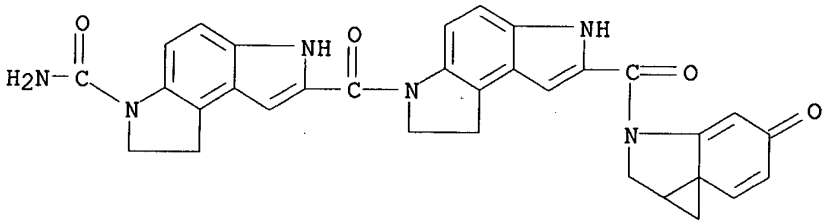

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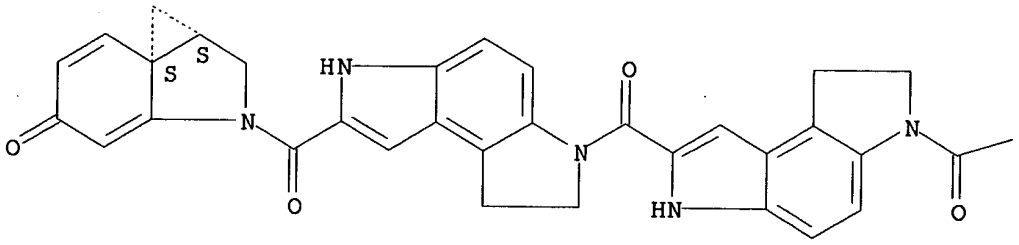
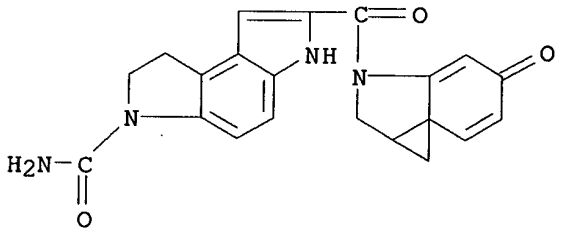
Absolute stereochemistry. Rotation (+).

PAGE 1-A



PAGE 1-B

RN 128050-92-0 HCAPLUS
CN Benzo[1,2-b:4,3-b']dipyrrole-3(2H)-carboxamide, 7-[(1a,2-dihydro-5-oxo-1H-cycloprop[c]indol-3(5H)-yl)carbonyl]-1,6-dihydro-, (1aR)- (9CI) (CA INDEX NAME)



RN 128050-93-1 HCAPLUS
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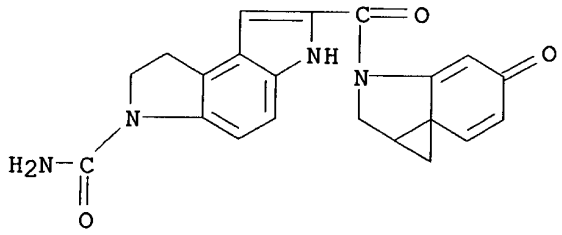
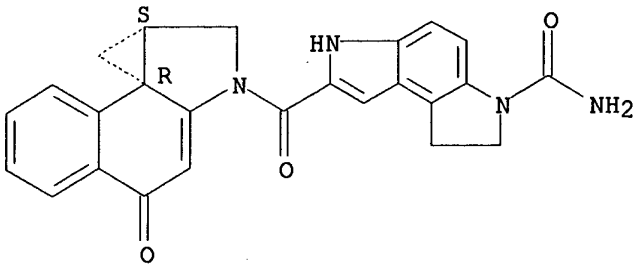


RN 128300-14-1 HCAPLUS

CN Benzo[1,2-b:4,3-b']dipyrrole-3(2H)-carboxamide, 7-[[(8bR,9aS)-9,9a-dihydro-4-oxo-1H-benzo[e]cycloprop[c]indol-2(4H)-yl]carbonyl]-1,6-dihydro- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 128300-15-2 HCAPLUS
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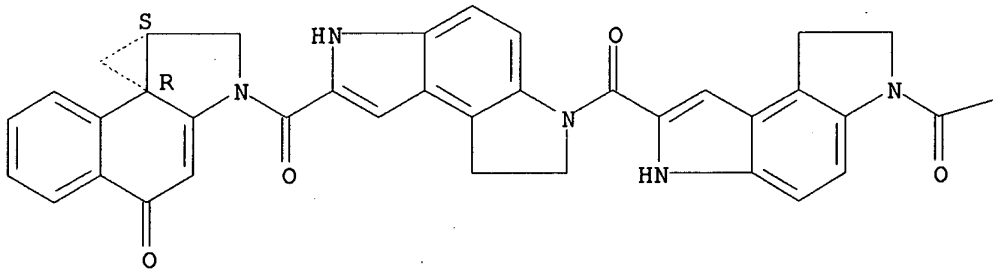
Absolute stereochemistry. Rotation (+).

PAGE 1-A

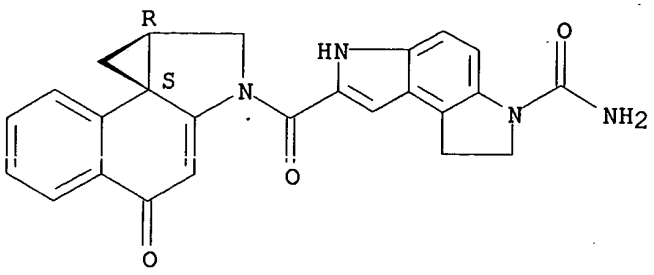


PAGE 1-B

—NH2

RN 128300-16-3 HCAPLUS
CN Benzo[1,2-b:4,3-b']dipyrrole-3(2H)-carboxamide, 7-[(9,9a-dihydro-4-oxo-1H-benzo[e]cycloprop[c]indol-2(4H)-yl)carbonyl]-1,6-dihydro-, (8bS)- (9CI) (CA INDEX NAME)

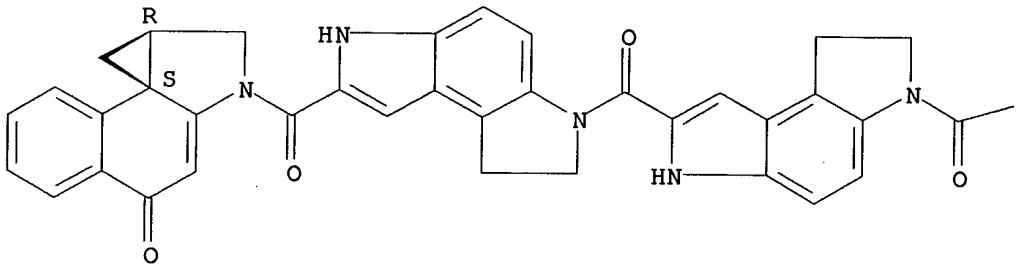
Absolute stereochemistry. Rotation (-).



RN 128300-17-4 HCAPLUS
CN Benzo[1,2-b:4,3-b']dipyrrole-3(2H)-carboxamide, 7-[[7-[(9,9a-dihydro-4-oxo-1H-benzo[e]cycloprop[c]indol-2(4H)-yl)carbonyl]-1,6-dihydrobenzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-1,6-dihydro-, (8bS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

PAGE 1-A



PAGE 1-B

—NH_2

RN 135306-52-4 HCAPLUS
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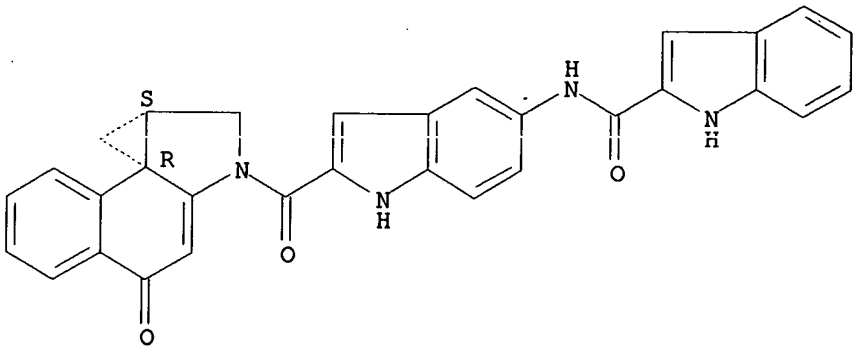
Absolute stereochemistry. Rotation (+).



RN 141781-45-5 HCAPLUS
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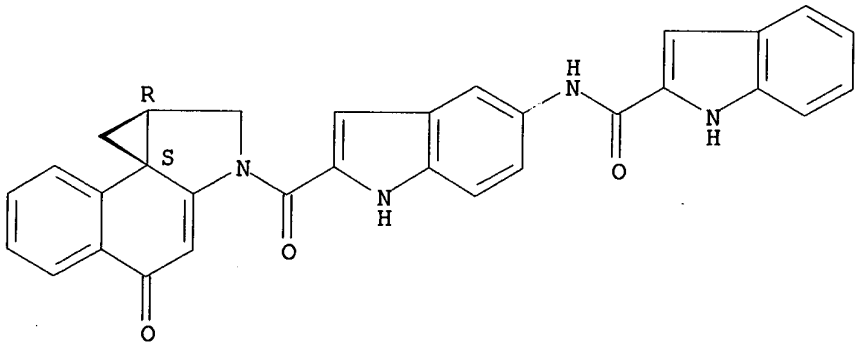
Absolute stereochemistry. Rotation (-).



RN 144224-62-4 HCAPLUS
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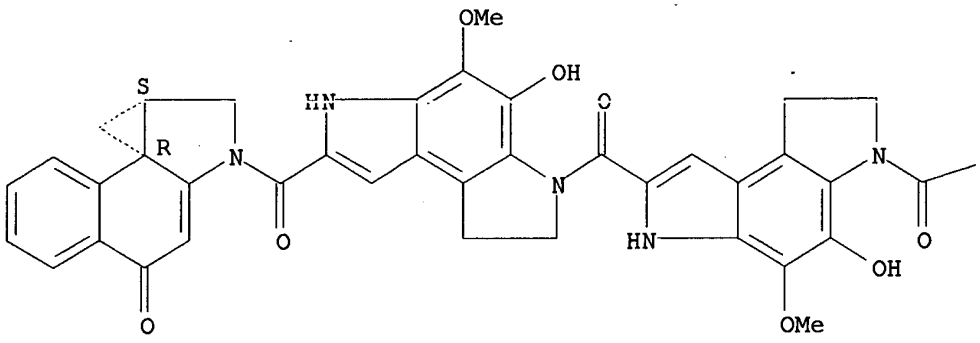
Absolute stereochemistry. Rotation (+).

PAGE 1-A



PAGE 1-B

—NH_2

RN 149251-66-1 HCAPLUS
CN Benzo[1,2-b:4,3-b']dipyrrole-3(2H)-carboxamide, 7-[[7-[(9,9a-dihydro-4-oxo-1H-benzo[e]cycloprop[c]indol-2(4H)-yl)carbonyl]-1,6-dihydro-4-hydroxy-5-methoxybenzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-1,6-dihydro-4-hydroxy-5-methoxy-, (8bS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

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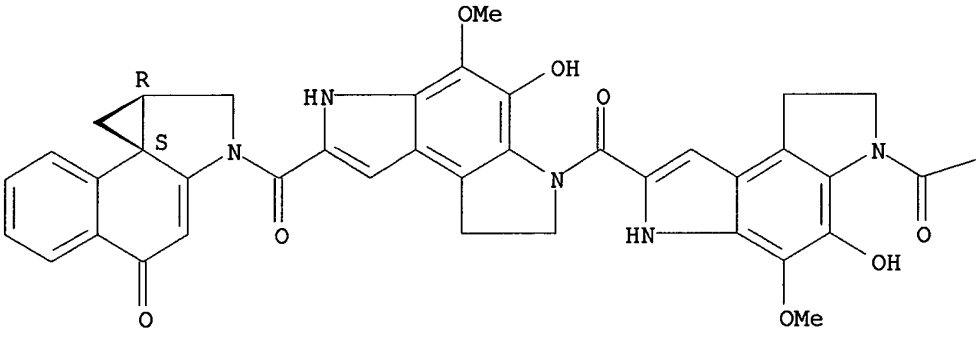
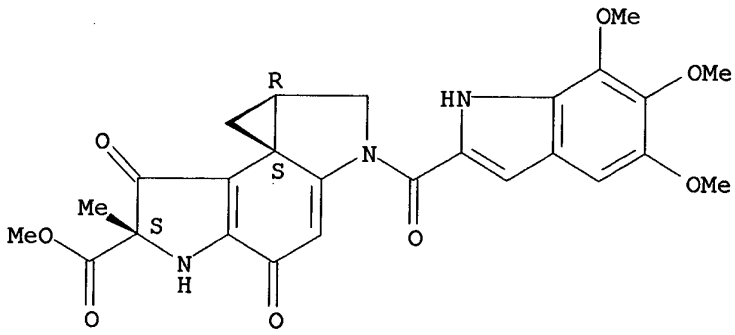


PAGE 1-B

—NH_2

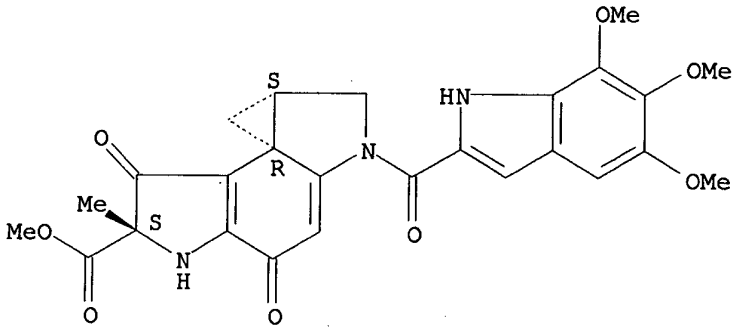
RN 149405-55-0 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,6,7,8,8a-octahydro-6-methyl-4,7-dioxo-2-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, methyl ester, (6S,7bS,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



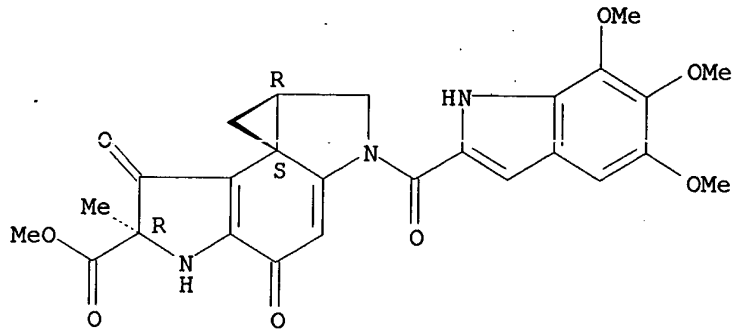
RN 149405-58-3 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,6,7,8,8a-octahydro-6-methyl-4,7-dioxo-2-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, methyl ester, (6S,7bR,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

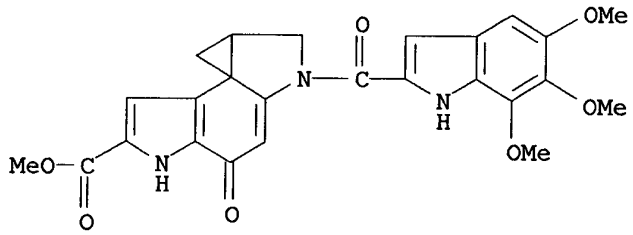


RN 149405-59-4 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,6,7,8,8a-octahydro-6-methyl-4,7-dioxo-2-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, methyl ester, (6R,7bS,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

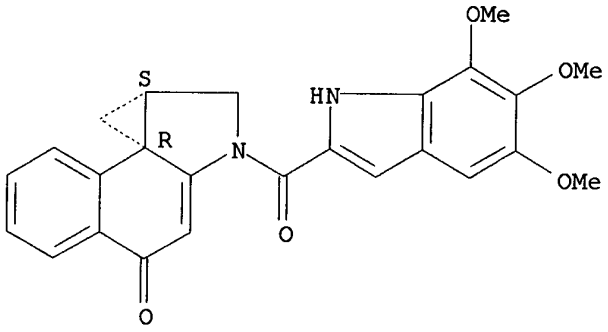


RN 151062-84-9 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,8,8a-hexahydro-4-oxo-2-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, methyl ester, (7bS,8aR)- (9CI) (CA INDEX NAME)



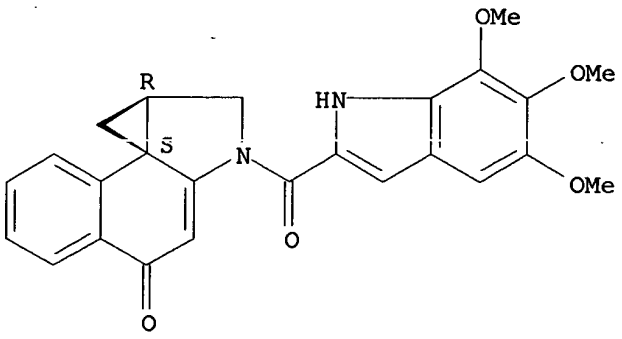
RN 157922-78-6 HCAPLUS
CN 4H-Benzo[e]cycloprop[c]indol-4-one, 1,2,9,9a-tetrahydro-2-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, (8bR,9aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 157968-94-0 HCAPLUS
CN 4H-Benzo[e]cycloprop[c]indol-4-one, 1,2,9,9a-tetrahydro-2-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, (8bS,9aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 160542-95-0 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 2-[[6-[[6-(aminocarbonyl)-3,6,7,8-tetrahydrobenzo[1,2-b:4,3-b']dipyrrol-2-yl]carbonyl]-3,6,7,8-tetrahydrobenzo[1,2-b:4,3-b']dipyrrol-2-yl]carbonyl]-1,2,4,5,8,8a-hexahydro-4-oxo-, methyl ester, (7bR,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

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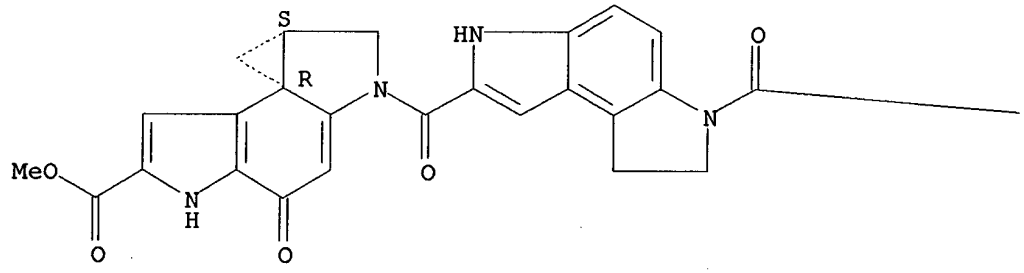

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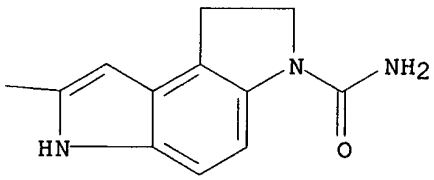

RN 160637-26-3 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 2-[[6-[[6-(aminocarbonyl)-3,6,7,8-tetrahydrobenzo[1,2-b:4,3-b']dipyrrol-2-yl]carbonyl]-3,6,7,8-tetrahydrobenzo[1,2-b:4,3-b']dipyrrol-2-yl]carbonyl]-1,2,4,5,8,8a-hexahydro-4-oxo-, methyl ester, (7bS,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

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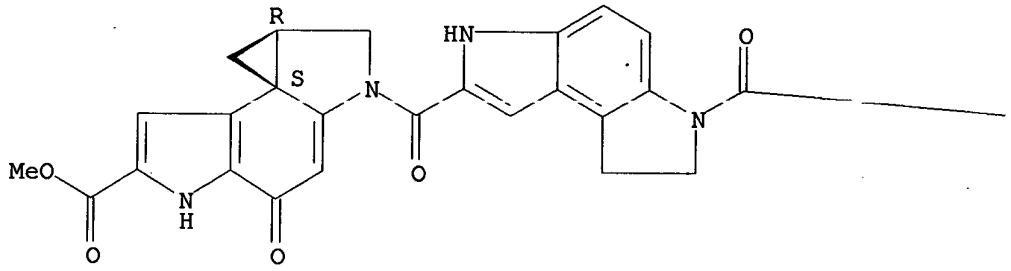

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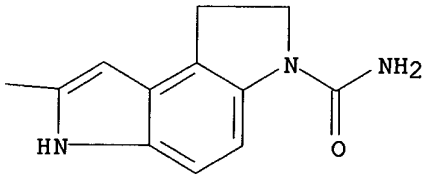
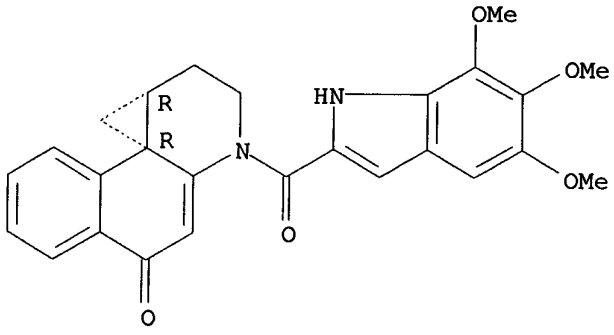


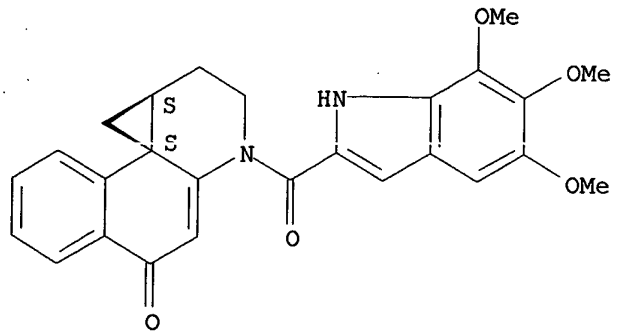
RN 161442-89-3 HCAPLUS
CN Benzo[f]cyclopropa[d]quinolin-5(1H)-one, 2,3,10,10a-tetrahydro-3-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, (9bR,10aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



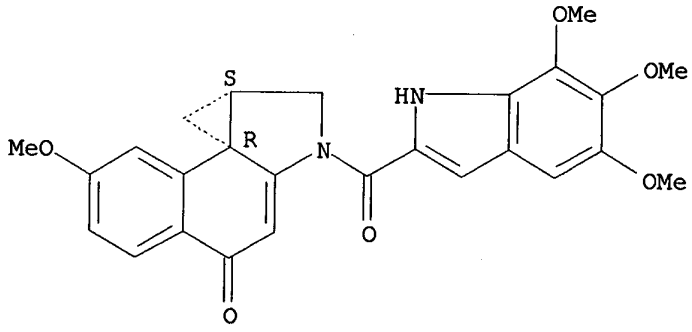
RN 161442-90-6 HCAPLUS
CN Benzo[f]cyclopropa[d]quinolin-5(1H)-one, 2,3,10,10a-tetrahydro-3-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, (9bS,10aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



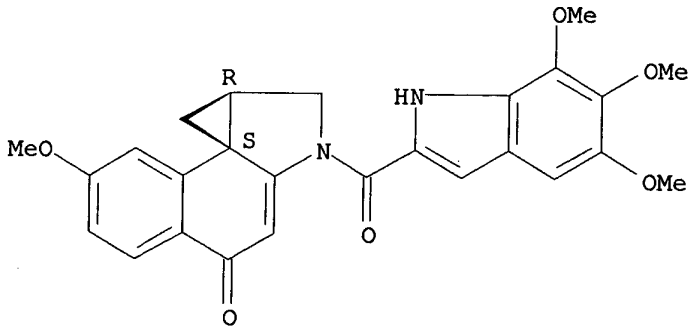
RN 173655-25-9 HCAPLUS
CN 4H-Benzo[e]cycloprop[c]indol-4-one, 1,2,9,9a-tetrahydro-7-methoxy-2-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, (8bR,9aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 173655-26-0 HCAPLUS
CN 4H-Benzo[e]cycloprop[c]indol-4-one, 1,2,9,9a-tetrahydro-7-methoxy-2-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, (8bS,9aR)- (9CI) (CA INDEX NAME)

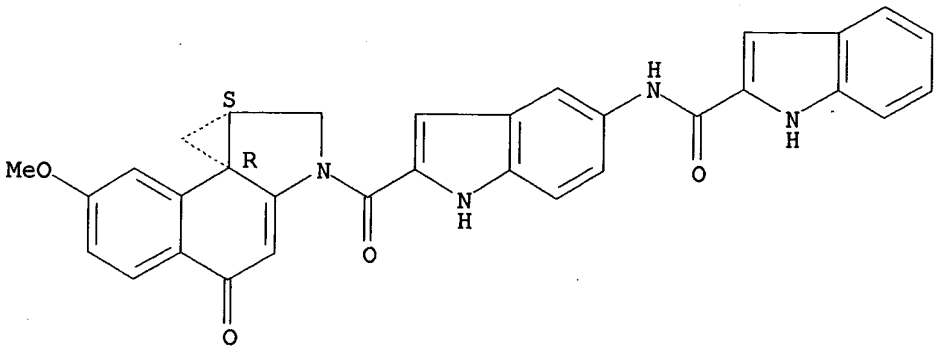
Absolute stereochemistry. Rotation (-).



RN 173655-27-1 HCAPLUS

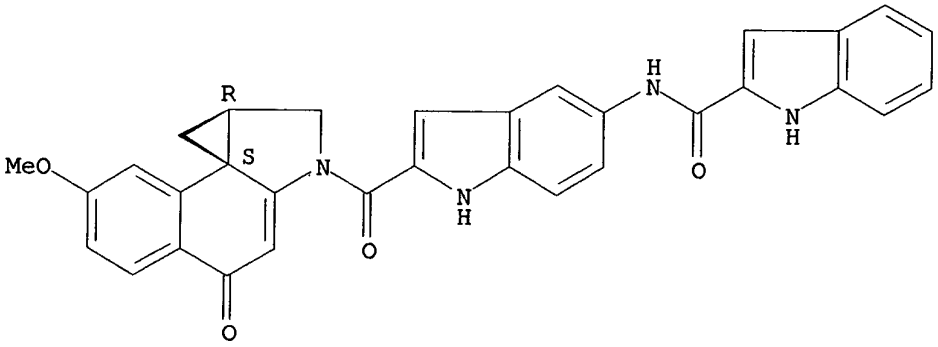
CN 1H-Indole-2-carboxamide, N-[2-[(9,9a-dihydro-7-methoxy-4-oxo-1H-benzo[e]cycloprop[c]indol-2(4H)-yl)carbonyl]-1H-indol-5-yl]-, (8bR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



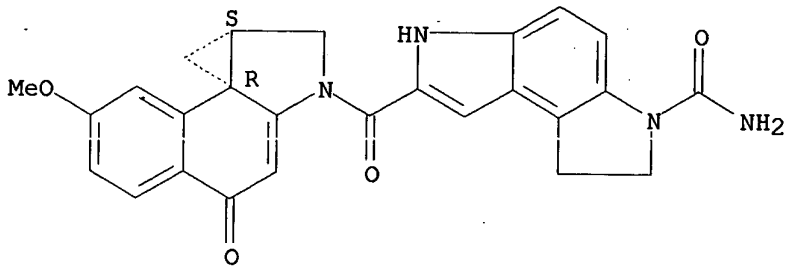
RN 173655-28-2 HCAPLUS
CN 1H-Indole-2-carboxamide, N-[2-[(9,9a-dihydro-7-methoxy-4-oxo-1H-benzo[e]cycloprop[c]indol-2(4H)-yl)carbonyl]-1H-indol-5-yl]-, (8bS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



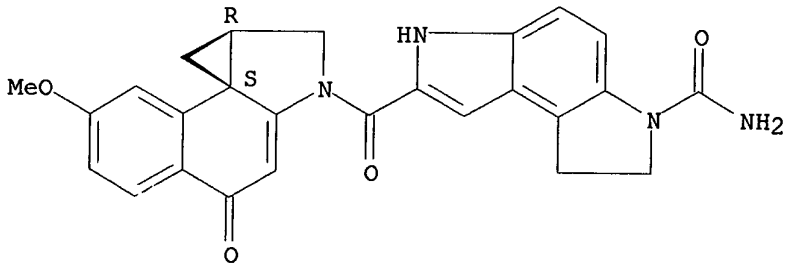
RN 173655-29-3 HCAPLUS
CN Benzo[1,2-b:4,3-b']dipyrrole-3(2H)-carboxamide, 7-[(9,9a-dihydro-7-methoxy-4-oxo-1H-benzo[e]cycloprop[c]indol-2(4H)-yl)carbonyl]-1,6-dihydro-, (8bR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 173655-30-6 HCAPLUS
CN Benzo[1,2-b:4,3-b']dipyrrole-3(2H)-carboxamide, 7-[(9,9a-dihydro-7-methoxy-4-oxo-1H-benzo[e]cycloprop[c]indol-2(4H)-yl)carbonyl]-1,6-dihydro-, (8bS)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 173655-31-7 HCAPLUS
CN Benzo[1,2-b:4,3-b']dipyrrole-3(2H)-carboxamide, 7-[[7-[(9,9a-dihydro-7-methoxy-4-oxo-1H-benzo[e]cycloprop[c]indol-2(4H)-yl)carbonyl]-1,6-dihydrobenzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-1,6-dihydro-, (8bR)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

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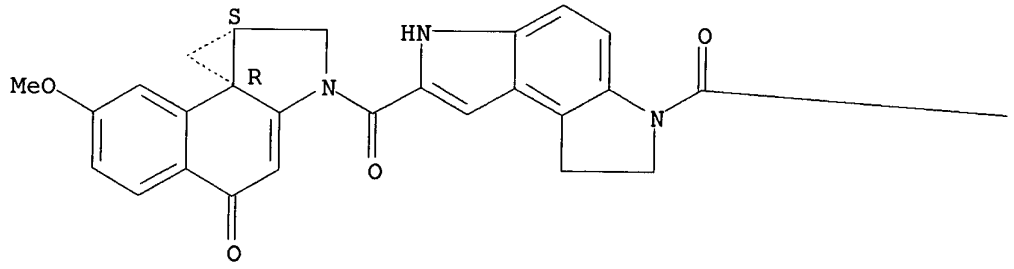

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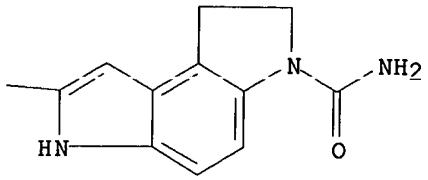

RN 173655-32-8 HCAPLUS
CN Benzo[1,2-b:4,3-b']dipyrrole-3(2H)-carboxamide, 7-[[7-[(9,9a-dihydro-7-methoxy-4-oxo-1H-benzo[e]cycloprop[c]indol-2(4H)-yl)carbonyl]-1,6-dihydrobenzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-1,6-dihydro-, (8bS)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

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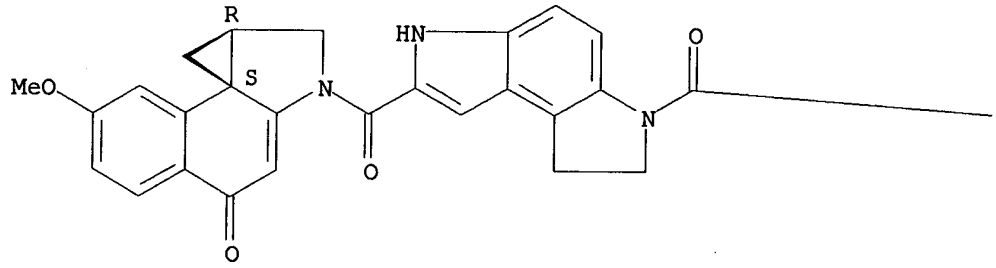

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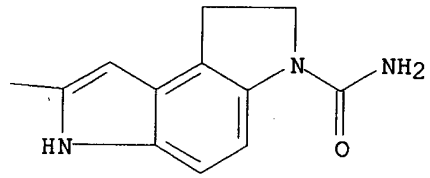
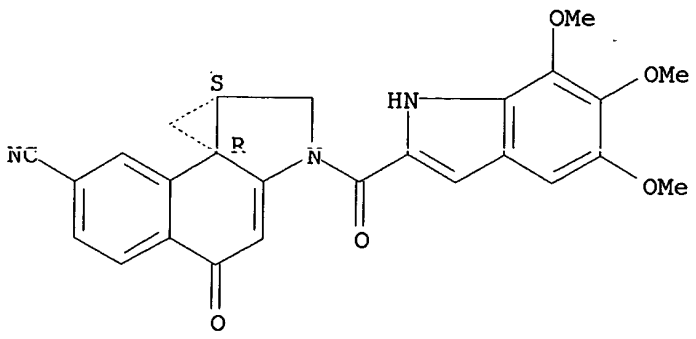


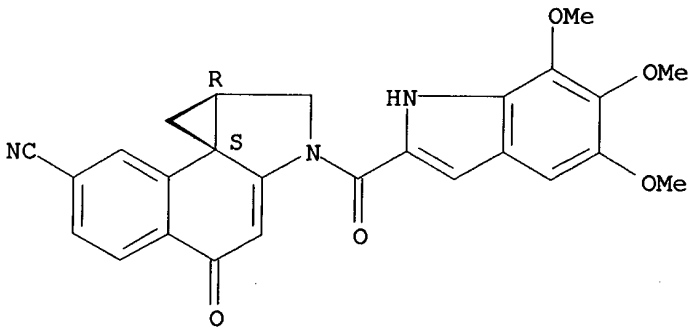
RN 178962-98-6 HCAPLUS
CN 1H-Benzo[e]cycloprop[c]indole-7-carbonitrile, 2,4,9,9a-tetrahydro-4-oxo-2-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, (8bR,9aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



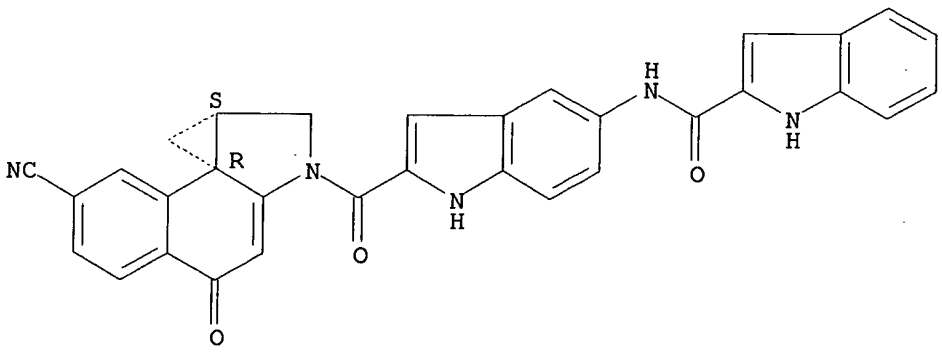
RN 178962-99-7 HCAPLUS
CN 1H-Benzo[e]cycloprop[c]indole-7-carbonitrile, 2,4,9,9a-tetrahydro-4-oxo-2-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, (8bS,9aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



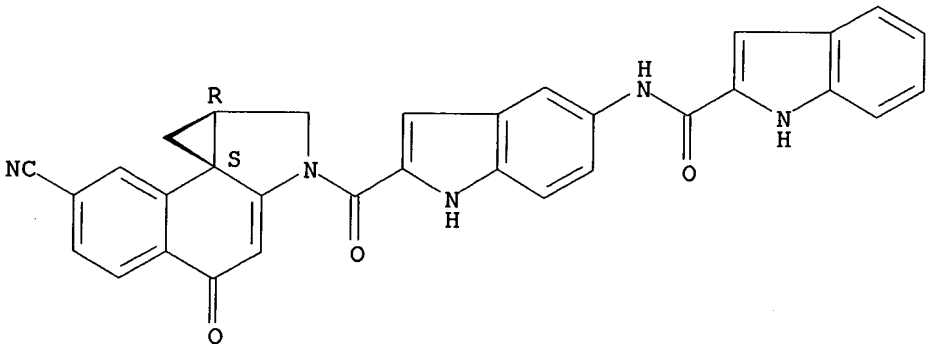
RN 178963-00-3 HCAPLUS
CN 1H-Indole-2-carboxamide, N-[2-[(7-cyano-9,9a-dihydro-4-oxo-1H-benzo[e]cycloprop[c]indol-2(4H)-yl)carbonyl]-1H-indol-5-yl]-, (8bR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



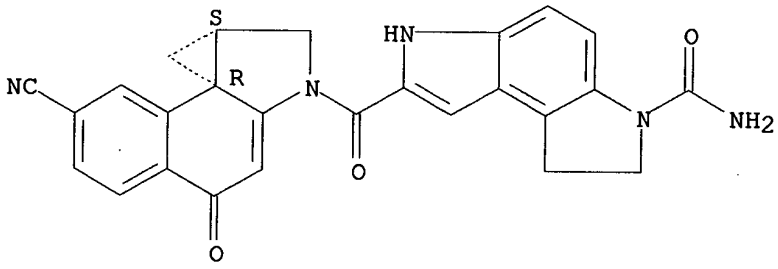
RN 178963-01-4 HCAPLUS
CN 1H-Indole-2-carboxamide, N-[2-[(7-cyano-9,9a-dihydro-4-oxo-1H-benzo[e]cycloprop[c]indol-2(4H)-yl)carbonyl]-1H-indol-5-yl]-, (8bS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



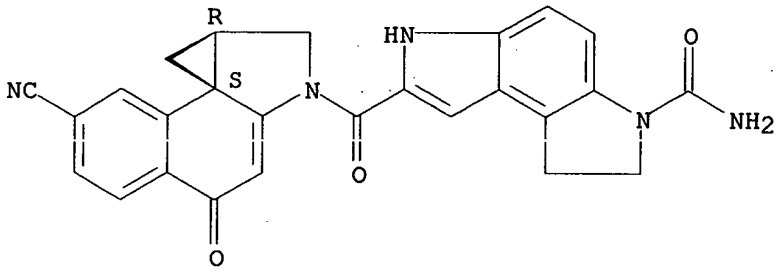
RN 178963-02-5 HCAPLUS
CN Benzo[1,2-b:4,3-b']dipyrrole-3(2H)-carboxamide, 7-[(7-cyano-9,9a-dihydro-4-oxo-1H-benzo[e]cycloprop[c]indol-2(4H)-yl)carbonyl]-1,6-dihydro-, (8bR)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

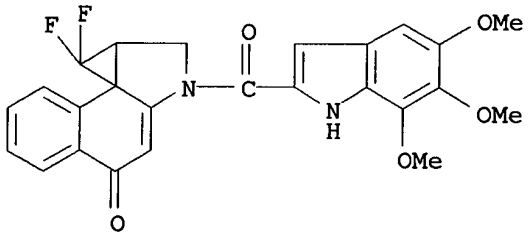


RN 178963-03-6 HCAPLUS
CN Benzo[1,2-b:4,3-b']dipyrrole-3(2H)-carboxamide, 7-[(7-cyano-9,9a-dihydro-4-oxo-1H-benzo[e]cycloprop[c]indol-2(4H)-yl)carbonyl]-1,6-dihydro-, (8bS)-(9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

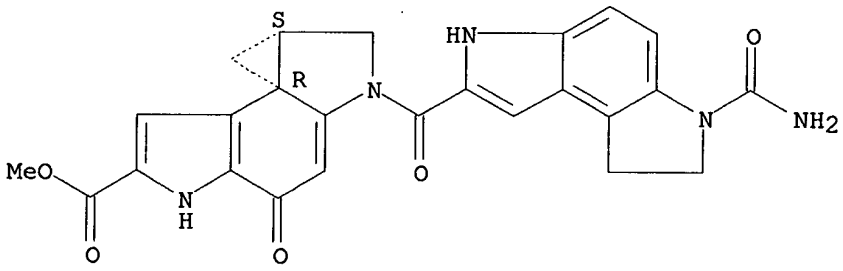


RN 181574-87-8 HCAPLUS
CN 4H-Benzo[e]cycloprop[c]indol-4-one, 9,9-difluoro-1,2,9,9a-tetrahydro-2-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]- (9CI) (CA INDEX NAME)



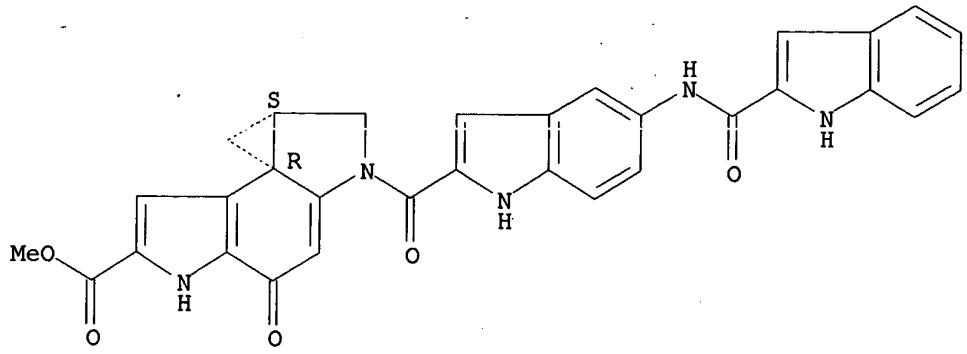
RN 190060-29-8 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 2-[[6-(aminocarbonyl)-3,6,7,8-tetrahydrobenzo[1,2-b:4,3-b']dipyrrol-2-yl]carbonyl]-1,2,4,5,8,8a-hexahydro-4-oxo-, methyl ester, (7bR,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



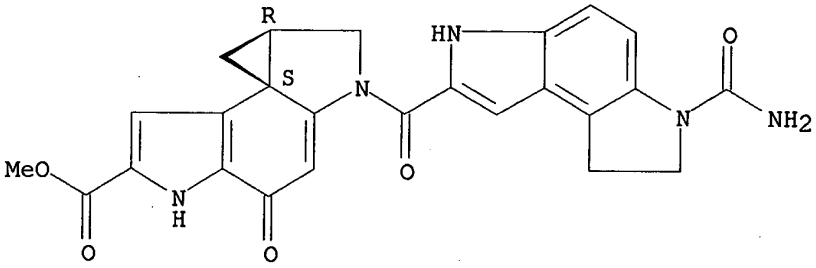
RN 190060-30-1 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,8,8a-hexahydro-2-[[5-[(1H-indol-2-ylcarbonyl)amino]-1H-indol-2-yl]carbonyl]-4-oxo-, methyl ester, (7bR,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



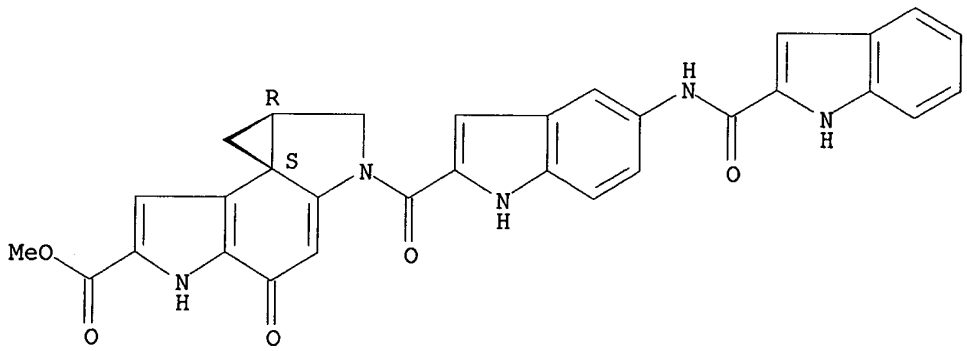
RN 190060-45-8 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 2-[[6-(aminocarbonyl)-3,6,7,8-tetrahydrobenzo[1,2-b:4,3-b']dipyrrol-2-yl]carbonyl]-1,2,4,5,8,8a-hexahydro-4-oxo-, methyl ester, (7bS,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 190060-46-9 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,8,8a-hexahydro-2-[[5-[(1H-indol-2-ylcarbonyl)amino]-1H-indol-2-yl]carbonyl]-4-oxo-, methyl ester, (7bS,8aR)- (9CI) (CA INDEX NAME)

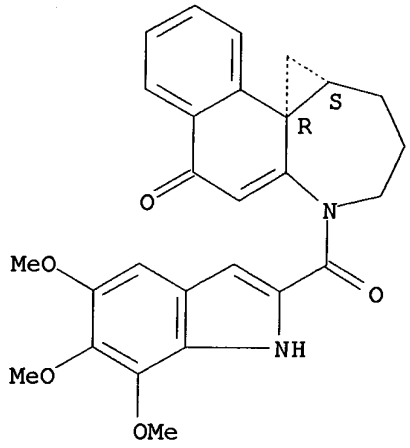
Absolute stereochemistry. Rotation (-).



RN 194222-35-0 HCAPLUS

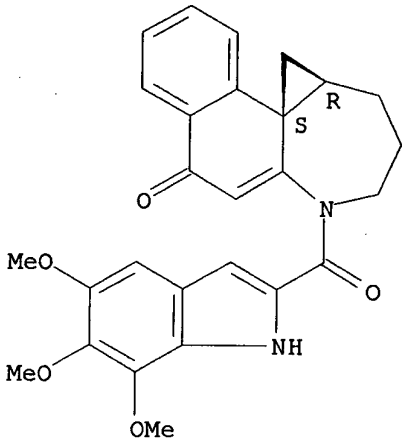
CN 6H-Cyclopropa[c]naphth[2,1-b]azepin-6-one, 1,2,3,4,11,11a-hexahydro-4-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, (10bR,11aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



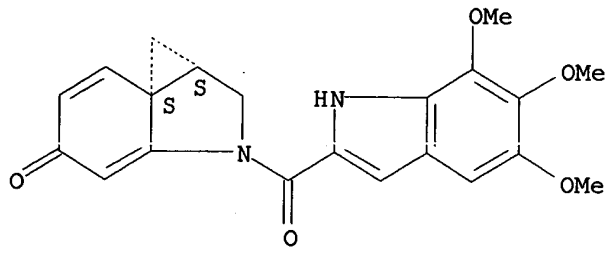
RN 194222-36-1 HCAPLUS
CN 6H-Cyclopropa[c]naphth[2,1-b]azepin-6-one, 1,2,3,4,11,11a-hexahydro-4-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, (10bS,11aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



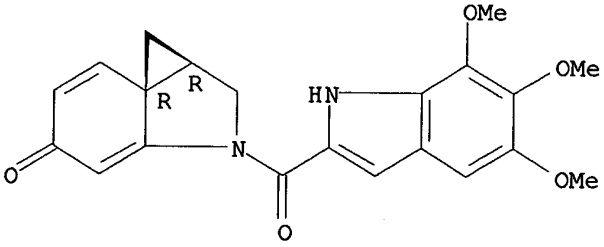
RN 194222-38-3 HCAPLUS
CN 5H-Cycloprop[c]indol-5-one, 1,1a,2,3-tetrahydro-3-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, (1aS,7aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

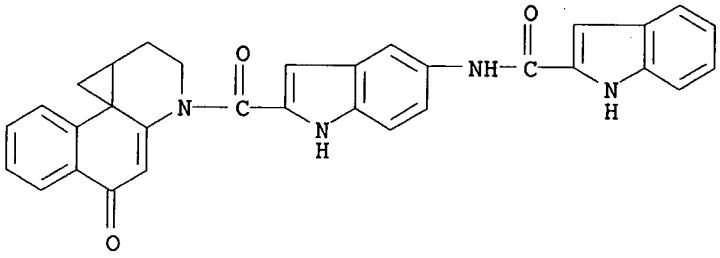


RN 194222-46-3 HCAPLUS
CN 5H-Cycloprop[c]indol-5-one, 1,1a,2,3-tetrahydro-3-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, (1aR,7aR)- (9CI) (CA INDEX NAME)

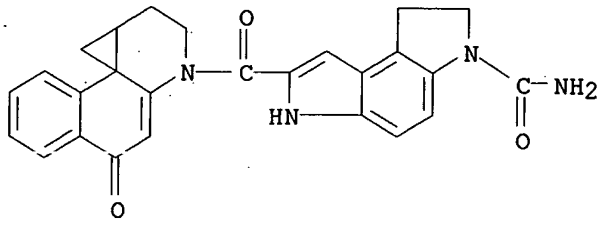
Absolute stereochemistry. Rotation (-).



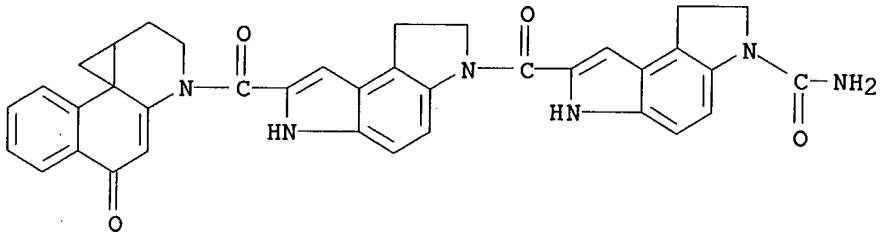
RN 198710-00-8 HCAPLUS
CN 1H-Indole-2-carboxamide, N-[2-[(1,2,10,10a-tetrahydro-5-oxobenzo[f]cyclopropa[d]quinolin-3(5H)-yl)carbonyl]-1H-indol-5-yl]- (9CI) (CA INDEX NAME)



RN 198710-03-1 HCAPLUS
CN Benzo[1,2-b:4,3-b']dipyrrole-3(2H)-carboxamide, 1,6-dihydro-7-[(1,2,10,10a-tetrahydro-5-oxobenzo[f]cyclopropa[d]quinolin-3(5H)-yl)carbonyl]- (9CI) (CA INDEX NAME)

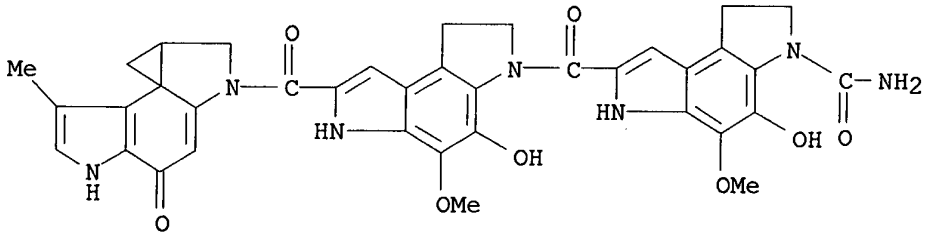


RN 198710-05-3 HCAPLUS
CN Benzo[1,2-b:4,3-b']dipyrrole-3(2H)-carboxamide, 7-[[1,6-dihydro-7-[(1,2,10,10a-tetrahydro-5-oxobenzo[f]cyclopropa[d]quinolin-3(5H)-yl)carbonyl]benzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-1,6-dihydro- (9CI) (CA INDEX NAME)



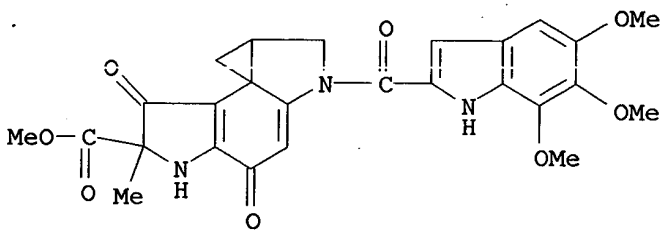
IT **69866-21-3DP**, (+)-CC-1065, analogs **118292-34-5DP**, (+)-Duocarmycin A, analogs **130288-24-3DP**, (+)-Duocarmycin SA, analogs
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(synthesis and evaluation of CC-1065 and duocarmycin analogs in **DNA** alkylation)

RN 69866-21-3 HCAPLUS
CN Benzo[1,2-b:4,3-b']dipyrrole-3(2H)-carboxamide, 7-[[1,6-dihydro-4-hydroxy-5-methoxy-7-[(4,5,8,8a-tetrahydro-7-methyl-4-oxocyclopropa[c]pyrrolo[3,2-e]indol-2(1H)-yl)carbonyl]benzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-1,6-dihydro-4-hydroxy-5-methoxy-, (7bR,8aS)- (9CI) (CA INDEX NAME)



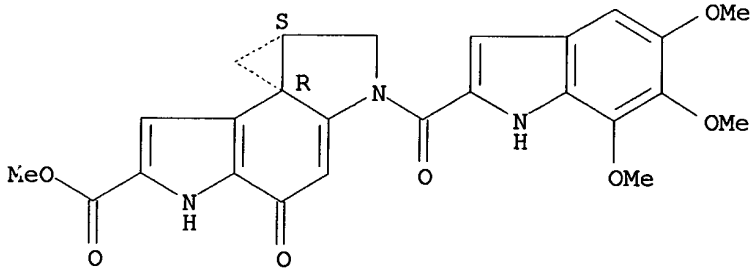
RN 118292-34-5 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,6,7,8,8a-octahydro-6-methyl-4,7-dioxo-2-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-

, methyl ester, (6R,7bR,8aS)- (9CI) (CA INDEX NAME)



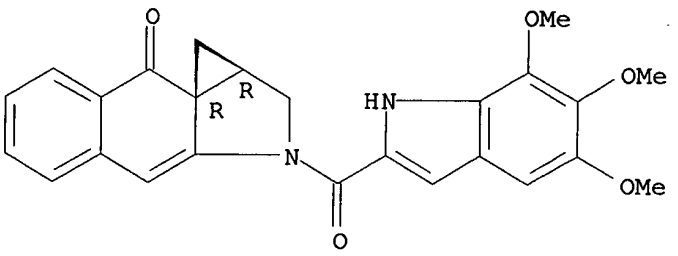
RN 130288-24-3 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,8,8a-hexahydro-4-oxo-2-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, methyl ester, (7bR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



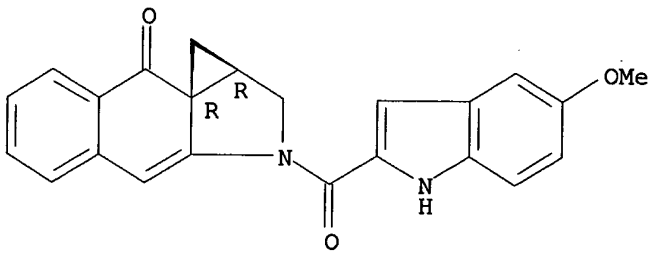
IT **198709-35-2P 198709-37-4P 198709-46-5P**
198709-50-1P 198709-54-5P 198709-58-9P
198709-62-5P 198709-66-9P 198709-72-7P
198709-75-0P 198709-79-4P 198709-83-0P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(synthesis and evaluation of CC-1065 and duocarmycin analogs in **DNA** alkylation)
RN 198709-35-2 HCAPLUS
CN 9H-Benzo[f]cycloprop[c]indol-9-one, 1,1a,2,3-tetrahydro-3-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, (1aR,9aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



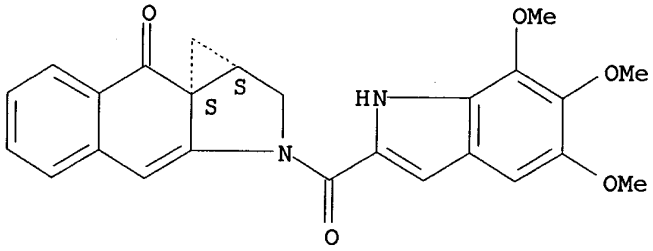
RN 198709-37-4 HCAPLUS
CN 9H-Benzo[f]cycloprop[c]indol-9-one, 1,1a,2,3-tetrahydro-3-[(5-methoxy-1H-indol-2-yl)carbonyl]-, (1aR,9aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



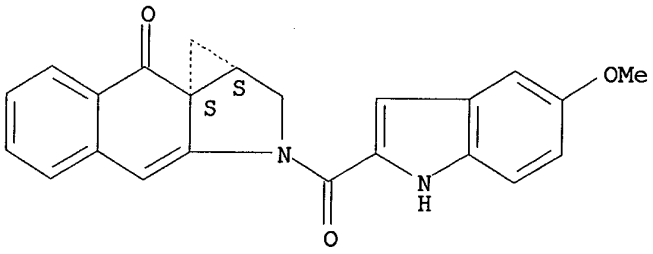
RN 198709-46-5 HCAPLUS
CN 9H-Benzo[f]cycloprop[c]indol-9-one, 1,1a,2,3-tetrahydro-3-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, (1aS,9aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



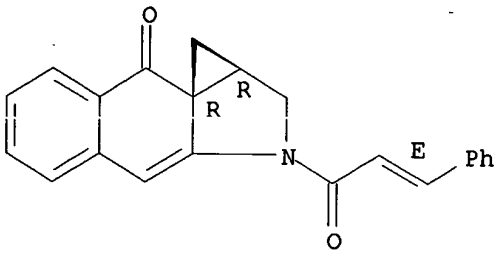
RN 198709-50-1 HCAPLUS
CN 9H-Benzo[f]cycloprop[c]indol-9-one, 1,1a,2,3-tetrahydro-3-[(5-methoxy-1H-indol-2-yl)carbonyl]-, (1aS,9aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



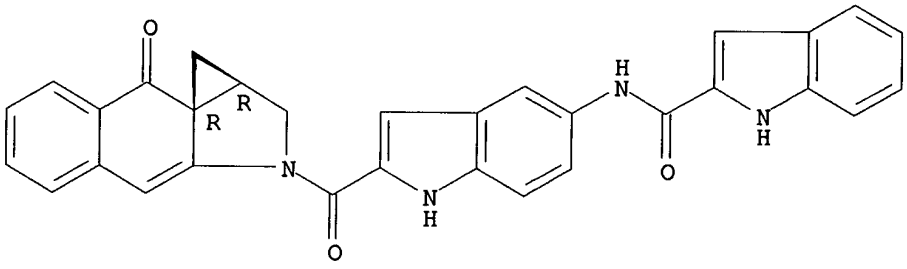
RN 198709-54-5 HCAPLUS
CN 9H-Benzo[f]cycloprop[c]indol-9-one, 1,1a,2,3-tetrahydro-3-(1-oxo-3-phenyl-2-propenyl)-, [1aR-[1aR*,3(E),9aR*]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).
Double bond geometry as shown.



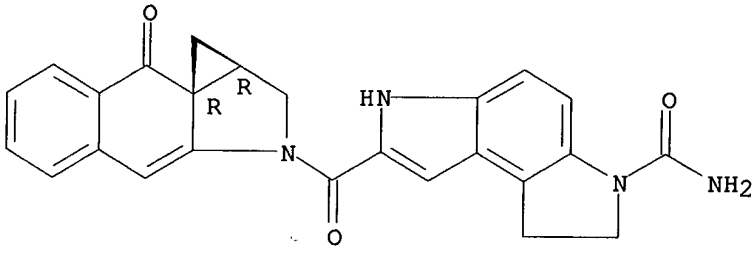
RN 198709-58-9 HCAPLUS
CN 1H-Indole-2-carboxamide, N-[2-[[(1aR,9aR)-1a,2-dihydro-9-oxo-1H-benzo[f]cycloprop[c]indol-3(9H)-yl]carbonyl]-1H-indol-5-yl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 198709-62-5 HCAPLUS
CN Benzo[1,2-b:4,3-b']dipyrrole-3(2H)-carboxamide, 7-[[(1aR,9aR)-1a,2-dihydro-9-oxo-1H-benzo[f]cycloprop[c]indol-3(9H)-yl]carbonyl]-1,6-dihydro- (9CI) (CA INDEX NAME)

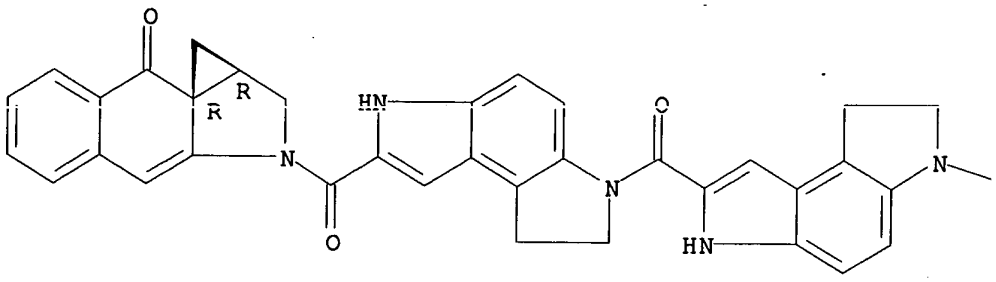
Absolute stereochemistry. Rotation (+).



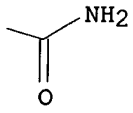
RN 198709-66-9 HCAPLUS
CN Benzo[1,2-b:4,3-b']dipyrrole-3(2H)-carboxamide, 7-[[7-[[(1aR,9aR)-1a,2-dihydro-9-oxo-1H-benzo[f]cycloprop[c]indol-3(9H)-yl]carbonyl]-1,6-dihydrobenzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-1,6-dihydro- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

PAGE 1-A

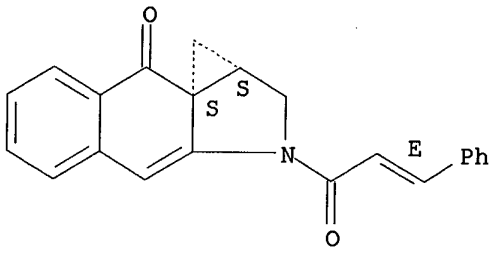


PAGE 1-B



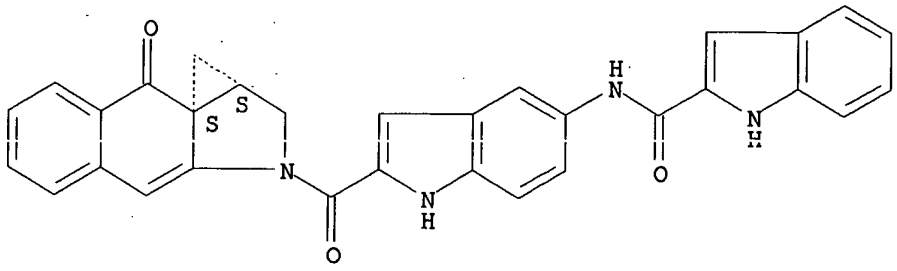
RN 198709-72-7 HCAPLUS
CN 9H-Benzo[f]cycloprop[c]indol-9-one, 1,1a,2,3-tetrahydro-3-(1-oxo-3-phenyl-2-propenyl)-, [1aS-[1aR*,3(E),9aR*]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).
Double bond geometry as shown.



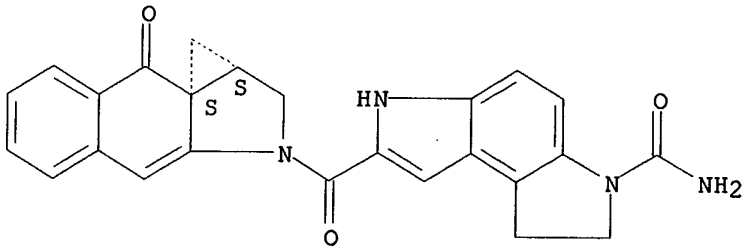
RN 198709-75-0 HCAPLUS
CN 1H-Indole-2-carboxamide, N-[2-[[(1aS,9aS)-1a,2-dihydro-9-oxo-1H-benzo[f]cycloprop[c]indol-3(9H)-yl]carbonyl]-1H-indol-5-yl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 198709-79-4 HCAPLUS
CN Benzo[1,2-b:4,3-b']dipyrrole-3(2H)-carboxamide, 7-[[(1aS,9aS)-1a,2-dihydro-9-oxo-1H-benzo[f]cycloprop[c]indol-3(9H)-yl]carbonyl]-1,6-dihydro- (9CI) (CA INDEX NAME)

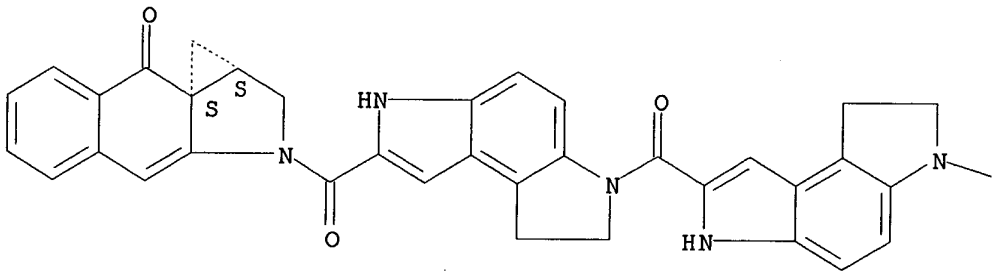
Absolute stereochemistry. Rotation (-).

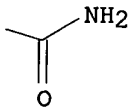


RN 198709-83-0 HCAPLUS
CN Benzo[1,2-b:4,3-b']dipyrrole-3(2H)-carboxamide, 7-[[7-[[(1aS,9aS)-1a,2-dihydro-9-oxo-1H-benzo[f]cycloprop[c]indol-3(9H)-yl]carbonyl]-1,6-dihydrobenzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-1,6-dihydro- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

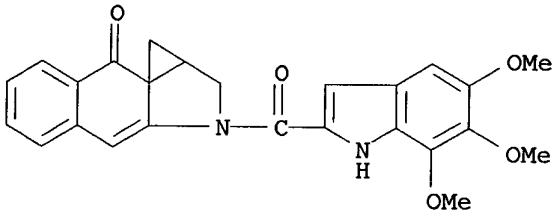
PAGE 1-A



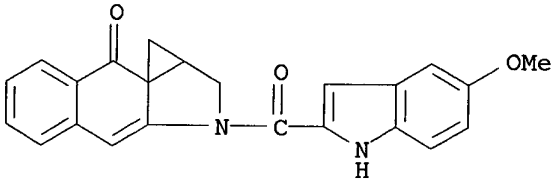


IT **198709-10-3P 198709-12-5P 198709-14-7P**
198709-16-9P 198709-18-1P 198709-20-5P
RL: SPN (Synthetic preparation); PREP (Preparation)
(synthesis and evaluation of CC-1065 and duocarmycin analogs in **DNA** alkylation)

RN 198709-10-3 HCAPLUS
CN 9H-Benzo[f]cycloprop[c]indol-9-one, 1,1a,2,3-tetrahydro-3-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]- (9CI) (CA INDEX NAME)

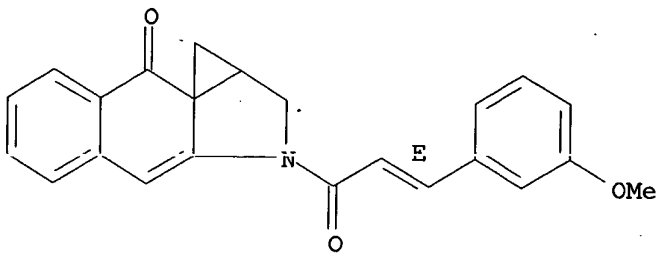


RN 198709-12-5 HCAPLUS
CN 9H-Benzo[f]cycloprop[c]indol-9-one, 1,1a,2,3-tetrahydro-3-[(5-methoxy-1H-indol-2-yl)carbonyl]- (9CI) (CA INDEX NAME)

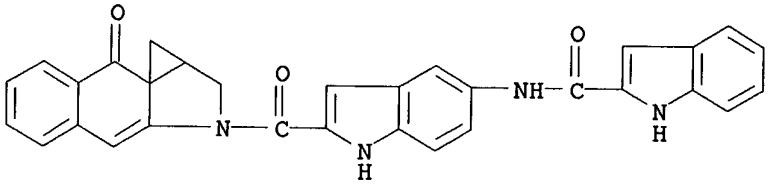


RN 198709-14-7 HCAPLUS
CN 9H-Benzo[f]cycloprop[c]indol-9-one, 1,1a,2,3-tetrahydro-3-[3-(3-methoxyphenyl)-1-oxo-2-propenyl]-, (E)- (9CI) (CA INDEX NAME)

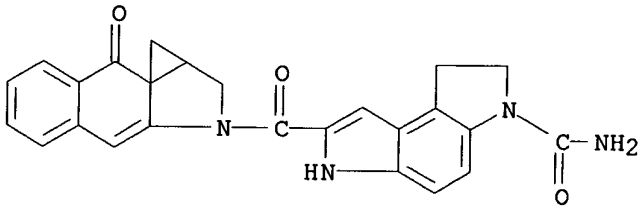
Double bond geometry as shown.



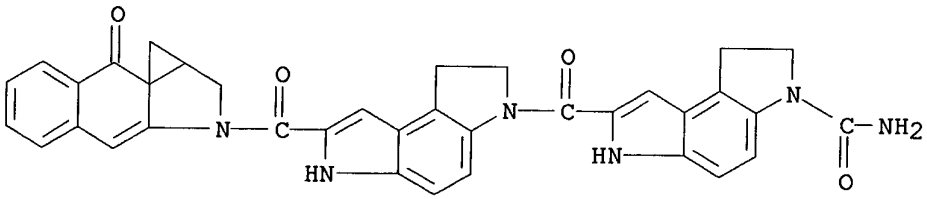
RN 198709-16-9 HCAPLUS
CN 1H-Indole-2-carboxamide, N-[2-[(1a,2-dihydro-9-oxo-1H-benzo[f]cycloprop[c]indol-3(9H)-yl)carbonyl]-1H-indol-5-yl]- (9CI) (CA INDEX NAME)



RN 198709-18-1 HCAPLUS
CN Benzo[1,2-b:4,3-b']dipyrrole-3(2H)-carboxamide, 7-[(1a,2-dihydro-9-oxo-1H-benzo[f]cycloprop[c]indol-3(9H)-yl)carbonyl]-1,6-dihydro- (9CI) (CA INDEX NAME)



RN 198709-20-5 HCAPLUS
CN Benzo[1,2-b:4,3-b']dipyrrole-3(2H)-carboxamide, 7-[[7-[(1a,2-dihydro-9-oxo-1H-benzo[f]cycloprop[c]indol-3(9H)-yl)carbonyl]-1,6-dihydrobenzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-1,6-dihydro- (9CI) (CA INDEX NAME)



L37 ANSWER 10 OF 21 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:645946 HCAPLUS
DOCUMENT NUMBER: 127:326047
TITLE: High resolution solution structure of a DNA duplex alkylated by the antitumor agent duocarmycin SA
AUTHOR(S): Eis, Peggy S.; Smith, Jarrod A.; Rydzewski, Jan M.; Case, David A.; Boger, Dale L.; Chazin, Walter J.
CORPORATE SOURCE: Department of Molecular Biology, The Scripps Research Institute, La Jolla, CA, 92037, USA
SOURCE: Journal of Molecular Biology (1997), 272(2), 237-252
CODEN: JMOBAK; ISSN: 0022-2836
PUBLISHER: Academic
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The three-dimensional soln. structure of duocarmycin SA in complex with d-(G1ACTAATTGAC11).cntdot.d-(G12TCATTAGTC22) has been detd. by restrained mol. dynamics and relaxation matrix calcns. using exptl. NOE distance and torsion angle constraints derived from 1H NMR spectroscopy. The final input data consisted of a total of 858 distance and 189 dihedral angle constraints, an av. of 46 constraints per residue. In the ensemble of 20 final structures, there were no distance constraint violations >0.06 .ANG. or torsion angle violations >0.8.degree.. The av. pairwise root mean square deviation (RMSD) over all 20 structures for the binding site region is 0.57 .ANG. (av. RMSD from the mean: 0.39 .ANG.). Although the DNA is very B-like, the sugar-phosphate backbone torsion angles .beta., .epsilon., and .zeta. are distorted from std. values in the binding site region. The structure reveals site-specific bonding of duocarmycin SA at the N3 position of adenine 19 in the AT-rich minor groove of the duplex and binding stabilization via hydrophobic interactions. Comparisons have been made to the structure of a closely related complex of duocarmycin A bound to an AT-rich DNA duplex. These results provide insights into crit. aspects of the alkylation site selectivity and source of catalysis of the DNA alkylating agents, and the unusual stability of the resulting adducts.

CC 1-6 (Pharmacology)

IT **Alkylation**
(biochem.; high resoln. soln. structure of DNA duplex alkylated by antitumor agent **duocarmycin** SA)

IT **118292-34-5**, Duocarmycin A
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(comparison with; high resoln. soln. structure of **DNA** duplex alkylated by antitumor agent duocarmycin SA)

IT **130288-24-3**, (+)-Duocarmycin SA
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(high resoln. soln. structure of **DNA** duplex alkylated by antitumor agent duocarmycin SA)

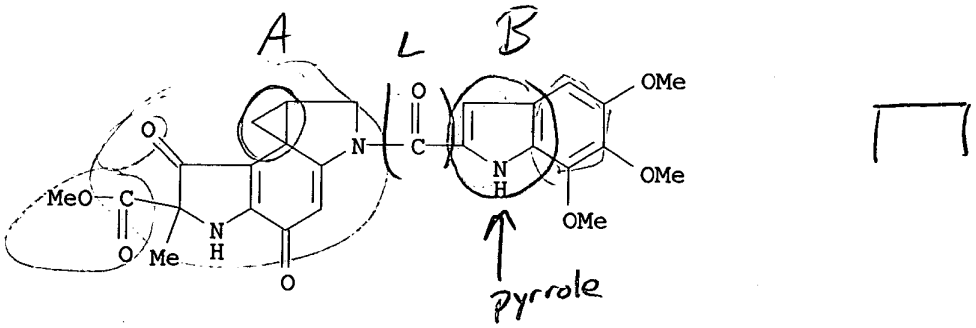
IT **130288-24-3D**, (+)-Duocarmycin SA, complexes with **DNA**
RL: BSU (Biological study, unclassified); MFM (Metabolic formation); PRP (Properties); BIOL (Biological study); FORM (Formation, nonpreparative)
(high resoln. soln. structure of **DNA** duplex alkylated by antitumor agent duocarmycin SA)

IT **118292-34-5**, Duocarmycin A
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(comparison with; high resoln. soln. structure of **DNA** duplex

alkylated by antitumor agent duocarmycin SA)

RN 118292-34-5 HCAPLUS

CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,6,7,8,8a-octahydro-6-methyl-4,7-dioxo-2-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, methyl ester, (6R,7bR,8aS)- (9CI) (CA INDEX NAME)



IT **130288-24-3**, (+)-Duocarmycin SA

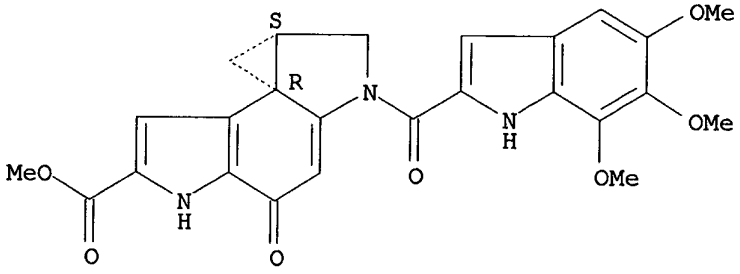
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(high resoln. soln. structure of **DNA** duplex alkylated by antitumor agent duocarmycin SA)

RN 130288-24-3 HCAPLUS

CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,8,8a-hexahydro-4-oxo-2-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, methyl ester, (7bR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **130288-24-3D**, (+)-Duocarmycin SA, complexes with **DNA**

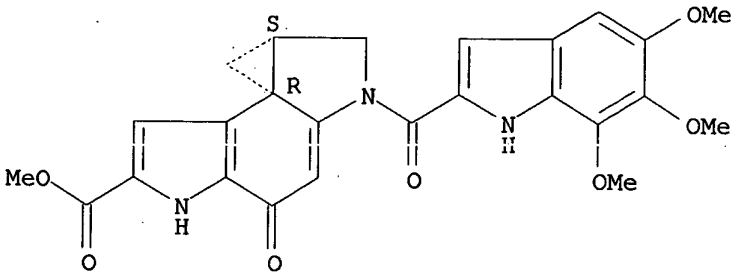
RL: BSU (Biological study, unclassified); MFM (Metabolic formation); PRP (Properties); BIOL (Biological study); FORM (Formation, nonpreparative)

(high resoln. soln. structure of **DNA** duplex alkylated by antitumor agent duocarmycin SA)

RN 130288-24-3 HCAPLUS

CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,8,8a-hexahydro-4-oxo-2-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, methyl ester, (7bR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L37 ANSWER 11 OF 21 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:324292 HCAPLUS
DOCUMENT NUMBER: 127:249
TITLE: Reversed and Sandwiched Analogs of Duocarmycin SA: Establishment of the Origin of the Sequence-Selective Alkylation of DNA and New Insights into the Source of Catalysis
AUTHOR(S): Boger, Dale L.; Bollinger, Bernd; Hertzog, Donald L.; Johnson, Douglas S.; Cai, Hui; Mesini, Philippe; Garbaccio, Robert M.; Jin, Qing; Kitos, Paul A.
CORPORATE SOURCE: Department of Chemistry, Scripps Research Institute, La Jolla, CA, 92037, USA
SOURCE: Journal of the American Chemical Society (1997), 119(21), 4987-4998
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The synthesis and examn. of two unique classes of duocarmycin SA analogs are described which we refer to as reversed and sandwiched analogs. Their examn. was found to establish both the origin of the DNA alkylation selectivity and that both enantiomers of this class of natural products are subject to the same polynucleotide recognition features. The most beautiful demonstration of this is the complete switch in the enantiomeric alkylation selectivity of the reversed analogs which is only consistent with the noncovalent binding model and incompatible with alkylation site models of the origin of the DNA alkylation selectivity. In addn., dramatic alterations in the rates of DNA alkylation were obsd. among the agents and correlate with the presence or absence of an extended, rigid N2 amide substituent. This has led to the proposal of a previously unrecognized source of catalysis for the DNA alkylation reaction which was introduced in the preceding paper of this issue (J. Am. Chem. Soc. 1997, 119, xxxx).

CC 1-3 (Pharmacology)
Section cross-reference(s): 6, 28

IT **Alkylation**
(biochem.; sequence-selective alkylation of DNA by reversed and sandwiched analogs of **duocarmycin** SA)

IT **160542-96-1P 160637-27-4P 190322-83-9P**
190322-85-1P 190322-87-3P 190322-93-1P
190322-95-3P 190323-04-7P 190323-08-1P
190323-10-5P 190323-12-7P 190323-13-8P
190323-15-0P 190323-16-1P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. and **DNA** alkylation by)

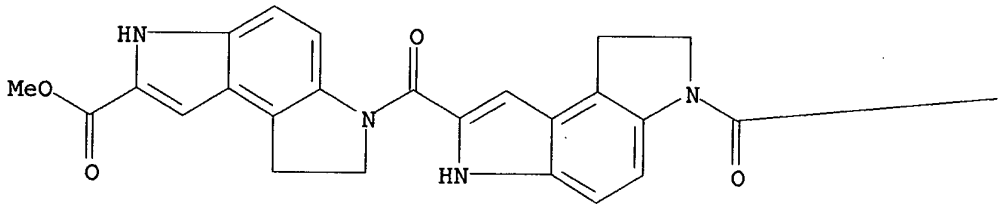
IT **190323-19-4P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. and **DNA** cyclization by)

IT **160542-96-1P 160637-27-4P 190322-83-9P**
190322-85-1P 190322-87-3P 190322-93-1P
190322-95-3P 190323-04-7P 190323-08-1P
190323-10-5P 190323-12-7P 190323-13-8P
190323-15-0P 190323-16-1P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. and **DNA** alkylation by)

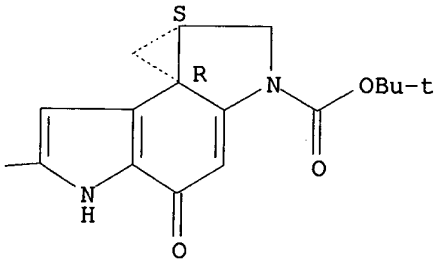
RN 160542-96-1 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-2(1H)-carboxylic acid, 6-[[7-[[1,6-dihydro-7-(methoxycarbonyl)benzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-1,6-dihydrobenzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-4,5,8,8a-tetrahydro-4-oxo-, 1,1-dimethylethyl ester, (7bR,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

PAGE 1-A



PAGE 1-B

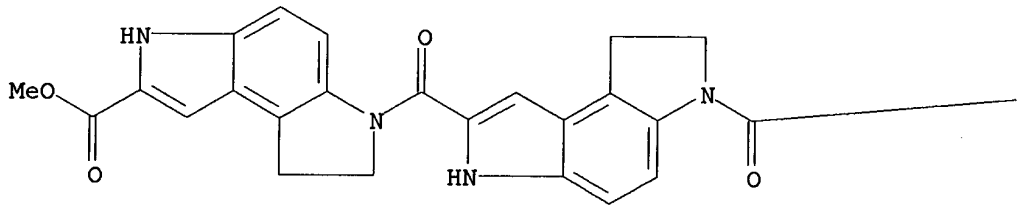


RN 160637-27-4 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-2(1H)-carboxylic acid, 6-[[7-[[1,6-dihydro-7-(methoxycarbonyl)benzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-1,6-dihydrobenzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-

4,5,8,8a-tetrahydro-4-oxo-, 1,1-dimethylethyl ester, (7bS,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

PAGE 1-A



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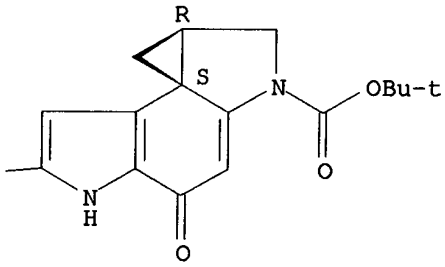
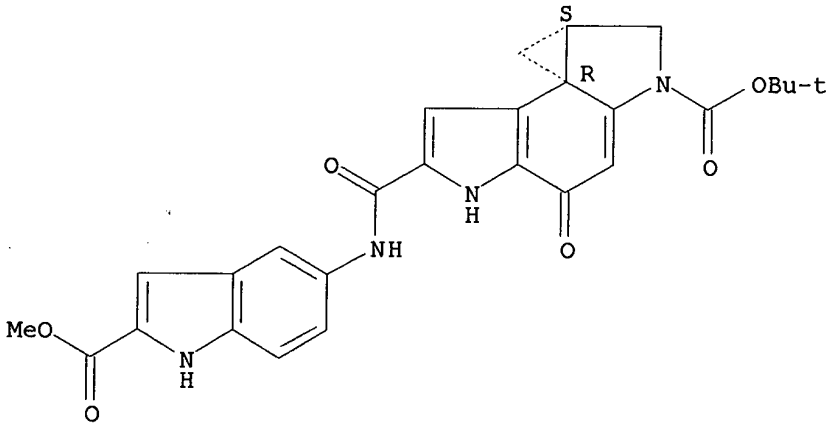


RN 190322-83-9 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-2(1H)-carboxylic acid, 4,5,8,8a-tetrahydro-6-[[[2-(methoxycarbonyl)-1H-indol-5-yl]amino]carbonyl]-4-oxo-, 1,1-dimethylethyl ester, (7bR,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

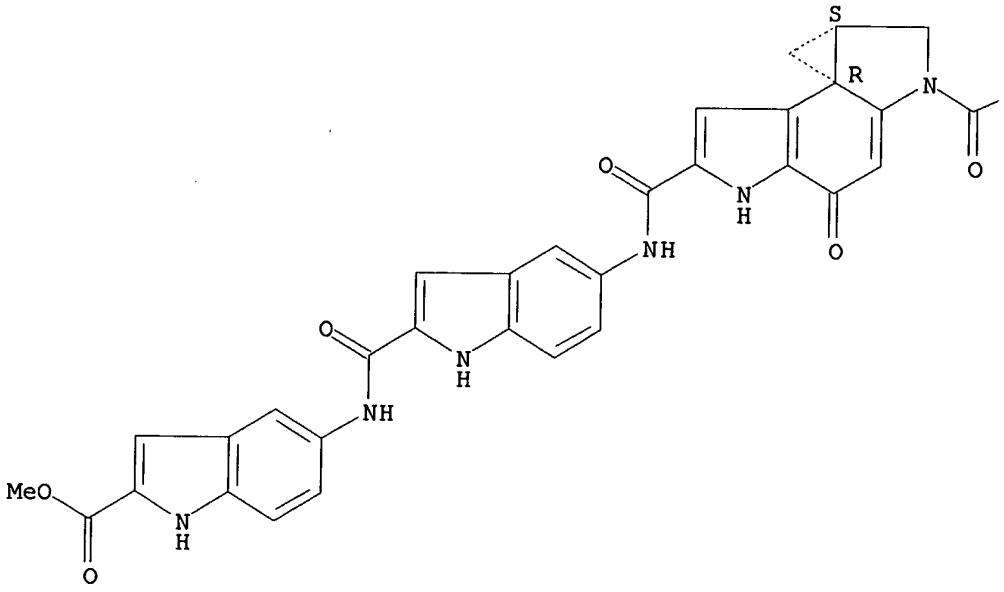


RN 190322-85-1 HCAPLUS

CN Cyclopropa[c]pyrrolo[3,2-e]indole-2(1H)-carboxylic acid, 4,5,8,8a-tetrahydro-6-[[[2-[[[2-(methoxycarbonyl)-1H-indol-5-yl]amino]carbonyl]-1H-indol-5-yl]amino]carbonyl]-4-oxo-, 1,1-dimethylethyl ester, (7bR,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

PAGE 1-A

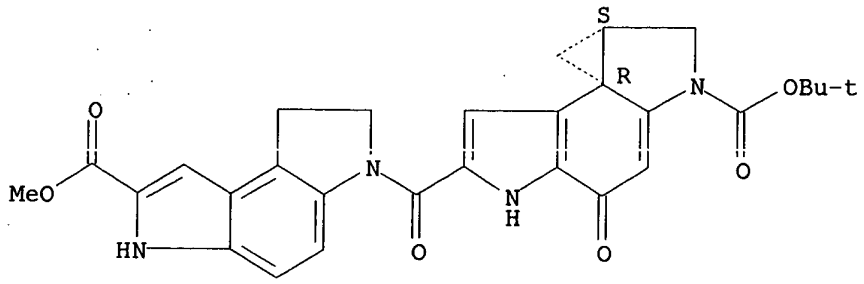


PAGE 1-B

OBu-t

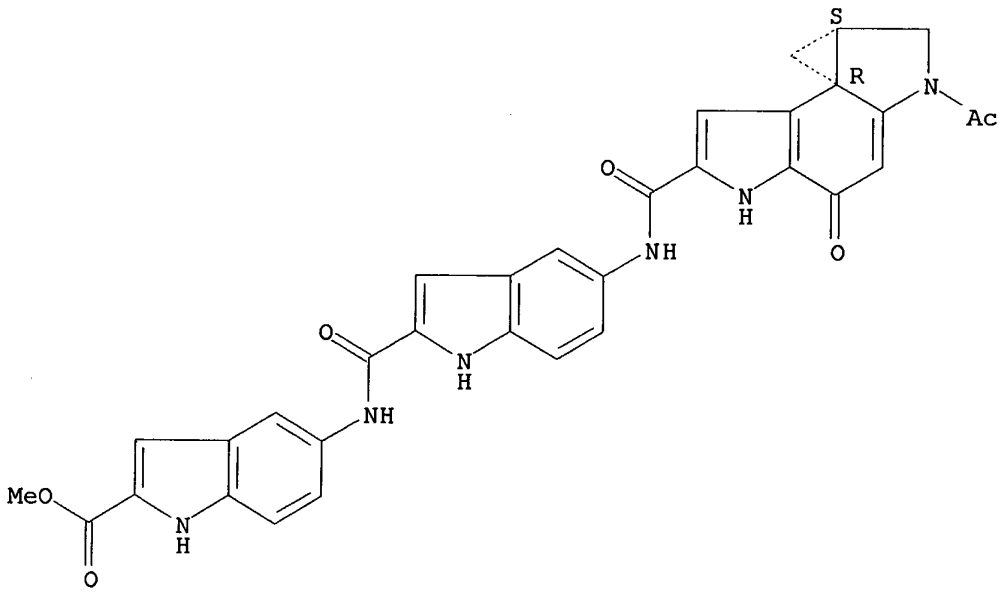
RN 190322-87-3 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-2(1H)-carboxylic acid, 6-[[1,6-dihydro-7-(methoxycarbonyl)benzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-4,5,8,8a-tetrahydro-4-oxo-, 1,1-dimethylethyl ester, (7bR,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



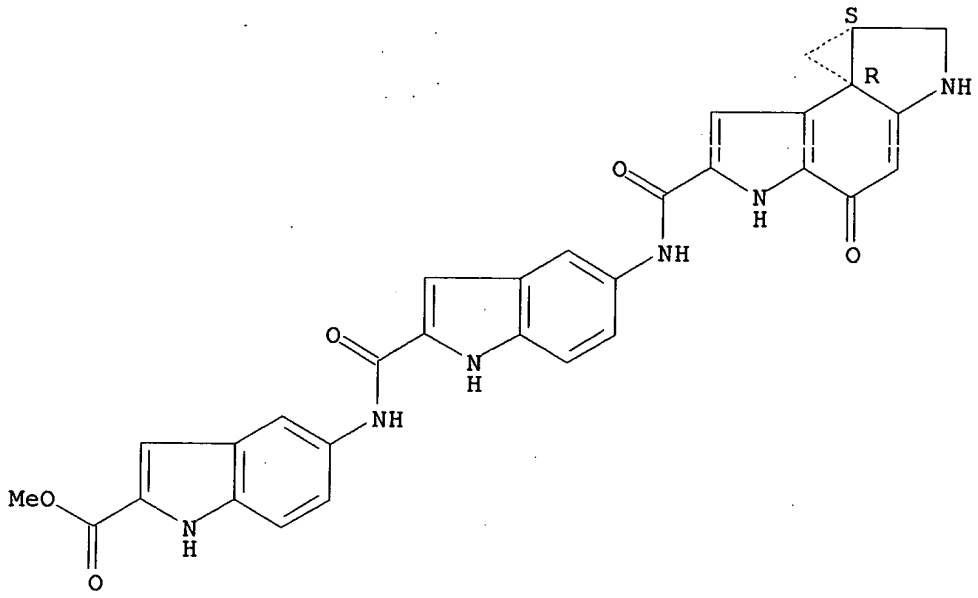
RN 190322-93-1 HCAPLUS
CN 1H-Indole-2-carboxylic acid, 5-[[[5-[[[(7bR,8aS)-2-acetyl-1,2,4,5,8,8a-hexahydro-4-oxocyclopropa[c]pyrrolo[3,2-e]indol-6-yl]carbonyl]amino]-1H-indol-2-yl]carbonyl]amino]-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 190322-95-3 HCAPLUS
CN 1H-Indole-2-carboxylic acid, 5-[[[5-[[[(7bR,8aS)-1,2,4,5,8,8a-hexahydro-4-oxocyclopropa[c]pyrrolo[3,2-e]indol-6-yl]carbonyl]amino]-1H-indol-2-yl]carbonyl]amino]-, methyl ester (9CI) (CA INDEX NAME)

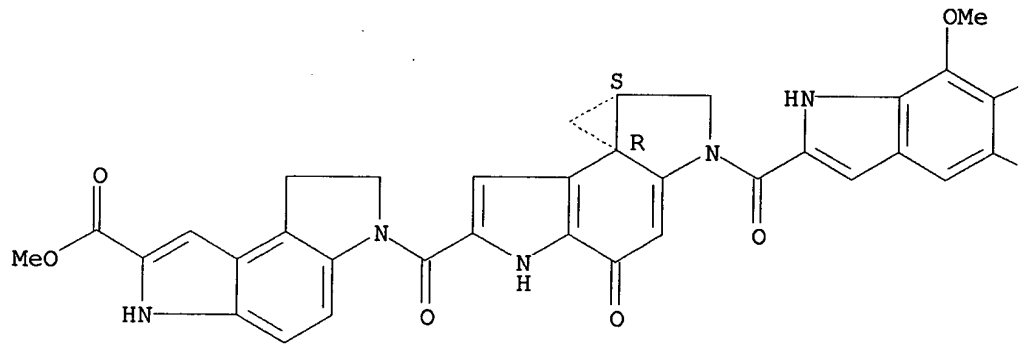
Absolute stereochemistry. Rotation (+).



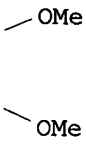
RN 190323-04-7 HCAPLUS
CN Benzo[1,2-b:4,3-b']dipyrrole-2-carboxylic acid, 6-[[(7bR,8aS)-1,2,4,5,8,8a-hexahydro-4-oxo-2-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]cyclopropa[c]pyrrolo[3,2-e]indol-6-yl]carbonyl]-3,6,7,8-tetrahydro-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

PAGE 1-A



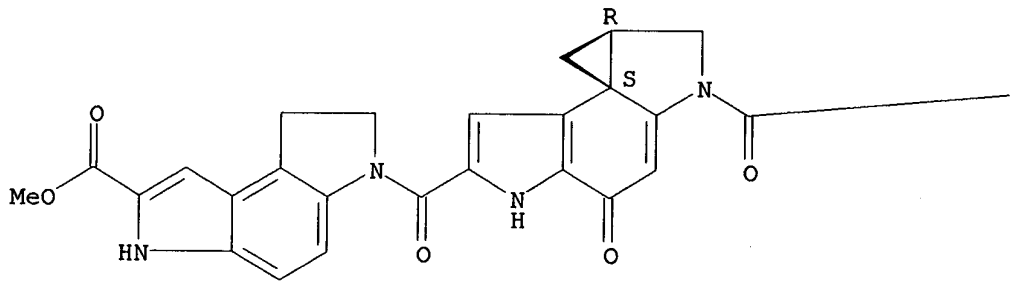
PAGE 1-B



RN 190323-08-1 HCAPLUS
CN Benzo[1,2-b:4,3-b']dipyrrole-2-carboxylic acid, 6-[[(7bS,8aR)-2-[[6-(aminocarbonyl)-3,6,7,8-tetrahydrobenzo[1,2-b:4,3-b']dipyrrol-2-yl]carbonyl]-1,2,4,5,8,8a-hexahydro-4-oxocyclopropa[c]pyrrolo[3,2-e]indol-6-yl]carbonyl]-3,6,7,8-tetrahydro-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

PAGE 1-A



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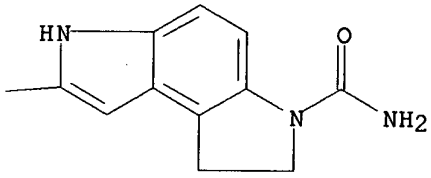
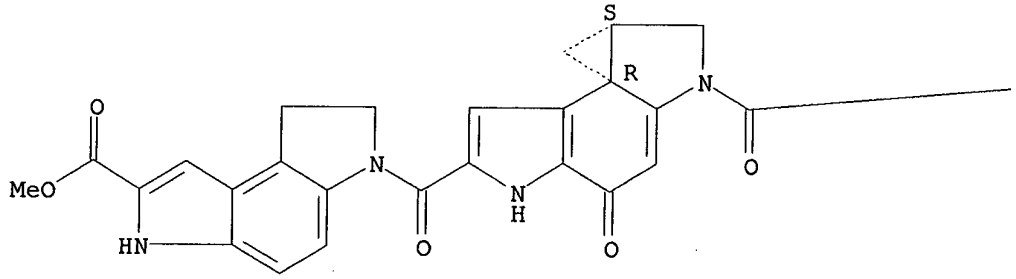
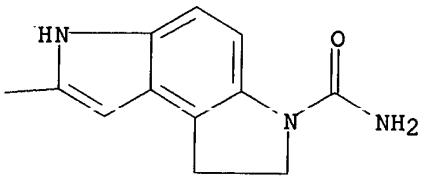


RN 190323-10-5 HCAPLUS
CN Benzo[1,2-b:4,3-b']dipyrrole-2-carboxylic acid, 6-[[(7bR,8aS)-2-[[6-(aminocarbonyl)-3,6,7,8-tetrahydrobenzo[1,2-b:4,3-b']dipyrrol-2-yl]carbonyl]-1,2,4,5,8,8a-hexahydro-4-oxocyclopropa[c]pyrrolo[3,2-e]indol-6-yl]carbonyl]-3,6,7,8-tetrahydro-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

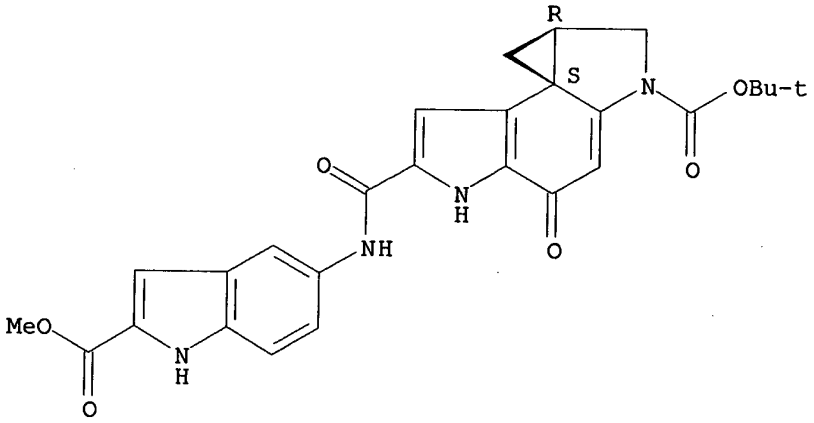
PAGE 1-A





RN 190323-12-7 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-2(1H)-carboxylic acid, 4,5,8,8a-tetrahydro-6-[[[2-(methoxycarbonyl)-1H-indol-5-yl]amino]carbonyl]-4-oxo-, 1,1-dimethylethyl ester, (7bS,8aR)- (9CI) (CA INDEX NAME)

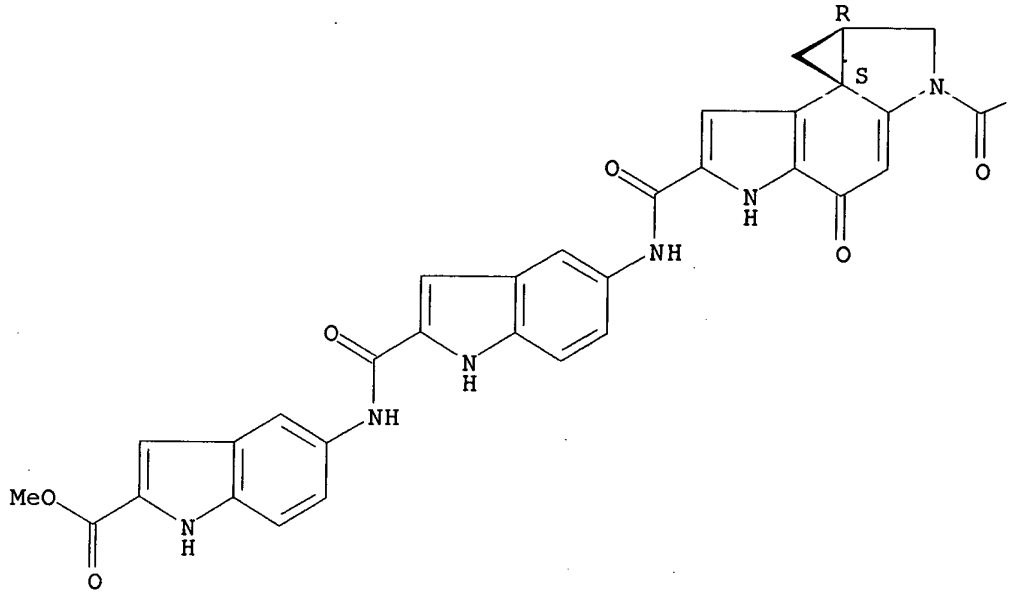
Absolute stereochemistry. Rotation (-).



RN 190323-13-8 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-2(1H)-carboxylic acid, 4,5,8,8a-tetrahydro-6-[[[2-[[[2-(methoxycarbonyl)-1H-indol-5-yl]amino]carbonyl]-1H-indol-5-yl]amino]carbonyl]-4-oxo-, 1,1-dimethylethyl ester, (7bS,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

PAGE 1-A

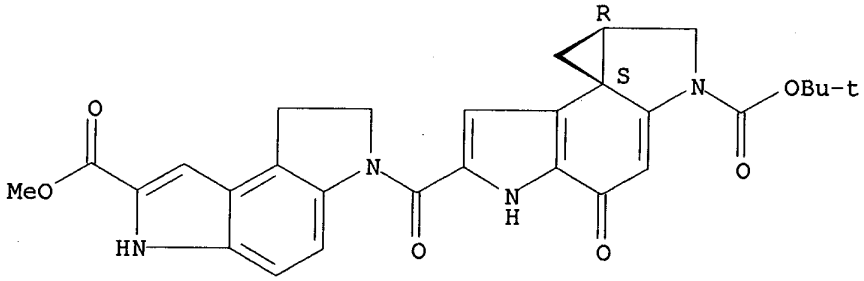


PAGE 1-B

OBu-t

RN 190323-15-0 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-2(1H)-carboxylic acid, 6-[[1,6-dihydro-7-(methoxycarbonyl)benzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-4,5,8,8a-tetrahydro-4-oxo-, 1,1-dimethylethyl ester, (7bS,8aR)- (9CI) (CA INDEX NAME)

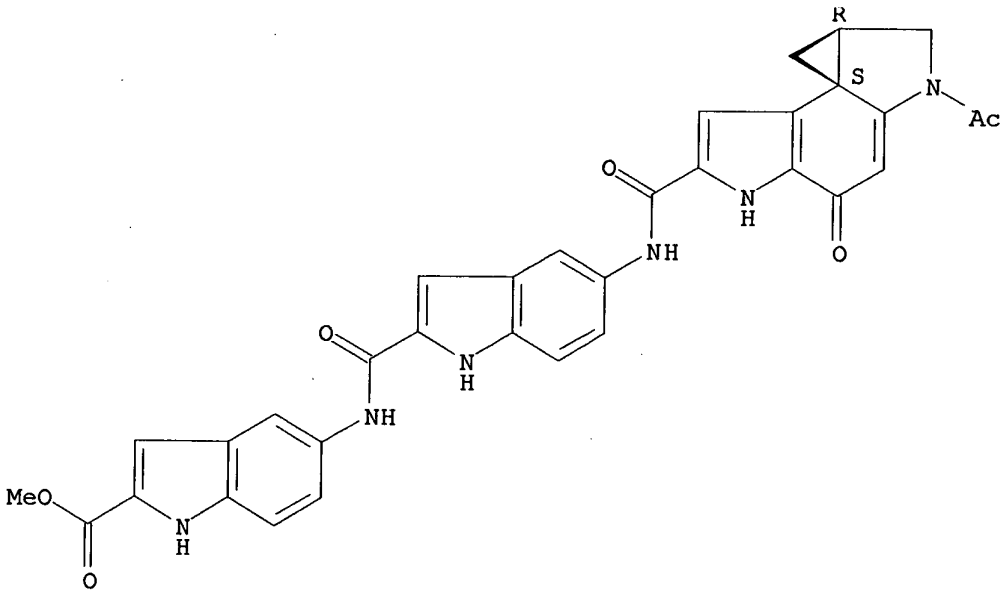
Absolute stereochemistry. Rotation (-).



RN 190323-16-1 HCAPLUS
CN 1H-Indole-2-carboxylic acid, 5-[[[5-[[[(7bS,8aR)-2-acetyl-1,2,4,5,8,8a-

hexahydro-4-oxocyclopropa[c]pyrrolo[3,2-e]indol-6-yl]carbonyl]amino]-1H-indol-2-yl]carbonyl]amino]-, methyl ester (9CI) (CA INDEX NAME)

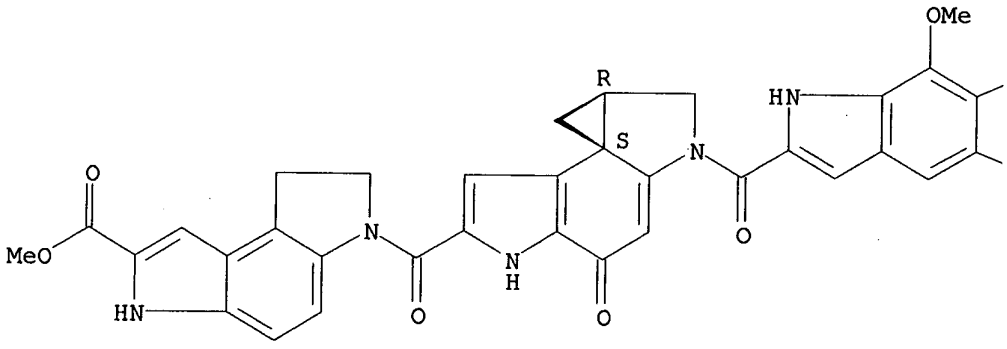
Absolute stereochemistry. Rotation (-).



IT **190323-19-4P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. and **DNA** cyclization by)
RN 190323-19-4 HCAPLUS
CN Benzo[1,2-b:4,3-b']dipyrrole-2-carboxylic acid, 6-[[(7bS,8aR)-1,2,4,5,8,8a-hexahydro-4-oxo-2-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]cyclopropa[c]pyrrolo[3,2-e]indol-6-yl]carbonyl]-3,6,7,8-tetrahydro-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

PAGE 1-A



L37 ANSWER 12 OF 21 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:324291 HCAPLUS
DOCUMENT NUMBER: 127:12962
TITLE: Duocarmycin SA shortened, simplified, and extended agents: a systematic examination of the role of the DNA binding subunit
AUTHOR(S): Boger, Dale L.; Hertzog, Donald L.; Bollinger, Bernd; Johnson, Douglas S.; Cai, Hui; Goldberg, Joel; Turnbull, Philip
CORPORATE SOURCE: Department of Chemistry, Scripps Research Institute, La Jolla, CA, 92037, USA
SOURCE: Journal of the American Chemical Society (1997), 119(21), 4977-4986
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The examn. of shortened, simplified, and extended analogs of duocarmycin SA are described and constitute a detailed study of the role of linked DNA binding subunit. In addn. to enhancing the DNA binding affinity and selectivity through minor groove noncovalent contacts, the studies in conjunction with those of the accompanying article illustrate that an extended rigid N2 amide substituent is required for catalysis of the DNA alkylation reaction. This activation for DNA alkylation is independent of pH, and we propose it results from a binding-induced conformational change in the agents which increases their inherent reactivity. The ground state destabilization of the substrate results from a twist in the linking amide that disrupts the vinylogous amide stabilization of the alkylation subunit and activates the agent for nucleophilic addn. This leads to preferential activation of the agents for DNA alkylation within the narrower, deeper AT-rich minor groove sites where the inherent twist in the linking amide and helical rise of the bound conformation is greatest. Thus, shape-selective recognition (preferential AT-rich noncovalent binding) and shape-dependent catalysis (induced twist in linking N2 amide) combine to restrict SN2 alkylation to accessible adenine N3 nucleophilic sites within the preferred binding sites. Addnl. ramifications of this DNA binding-induced conformational change on the reversibility of the DNA alkylation reaction are discussed. The results of the study illustrate the importance of the C5' methoxy group and the C6 Me ester of duocarmycin SA, and a previously unrecognized role for these substituents is proposed.

CC 1-3 (Pharmacology)
Section cross-reference(s): 25, 27

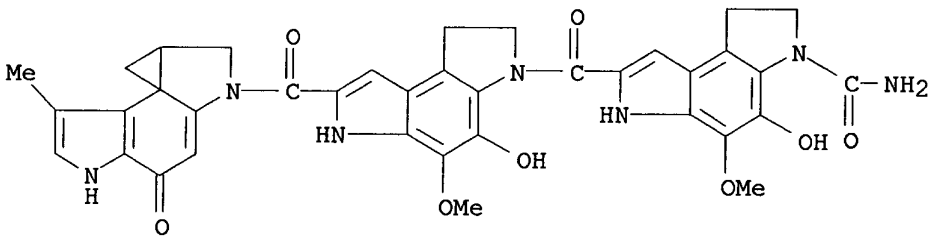
IT **Alkylation**
(DNA; **duocarmycin** SA shortened, simplified, and extended agents: a systematic examn. of the role of the DNA binding subunit)

IT **69866-21-3**, (+)-CC-1065 **118292-34-5**, (+)-Duocarmycin A
130288-24-3, (+)-Duocarmycin SA
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(duocarmycin SA shortened, simplified, and extended agents: a systematic examn. of the role of the **DNA** binding subunit)

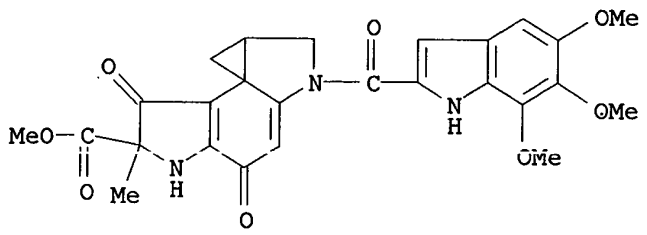
IT 1477-50-5P, 1H-Indole-2-carboxylic acid 4382-54-1P 16732-73-3P
24610-33-1P **110352-07-3P** 128049-55-8P 150992-82-8P
151062-83-8P **151062-84-9P** 151062-86-1P **160542-95-0P**
160637-26-3P 167167-41-1P 174955-96-5P **182957-16-0P**
182957-17-1P **182957-18-2P** **182957-19-3P**
182957-20-6P 182957-21-7P 182957-22-8P 182957-23-9P 190060-23-2P
190060-24-3P 190060-25-4P 190060-26-5P 190060-27-6P 190060-28-7P
190060-29-8P **190060-30-1P** **190060-31-2P**
190060-32-3P **190060-33-4P** 190060-34-5P 190060-35-6P
190060-36-7P 190060-37-8P 190060-38-9P 190060-39-0P 190060-40-3P
190060-41-4P 190060-42-5P 190060-43-6P 190060-44-7P
190060-45-8P **190060-46-9P** 190601-93-5P 190602-02-9P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(duocarmycin SA shortened, simplified, and extended agents: a systematic examn. of the role of the **DNA** binding subunit)

IT **69866-21-3**, (+)-CC-1065 **118292-34-5**, (+)-Duocarmycin A
130288-24-3, (+)-Duocarmycin SA
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(duocarmycin SA shortened, simplified, and extended agents: a systematic examn. of the role of the **DNA** binding subunit)

RN 69866-21-3 HCAPLUS
CN Benzo[1,2-b:4,3-b']dipyrrole-3(2H)-carboxamide, 7-[[1,6-dihydro-4-hydroxy-5-methoxy-7-[(4,5,8,8a-tetrahydro-7-methyl-4-oxocyclopropa[c]pyrrolo[3,2-e]indol-2(1H)-yl)carbonyl]benzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-1,6-dihydro-4-hydroxy-5-methoxy-, (7bR,8aS)- (9CI) (CA INDEX NAME)

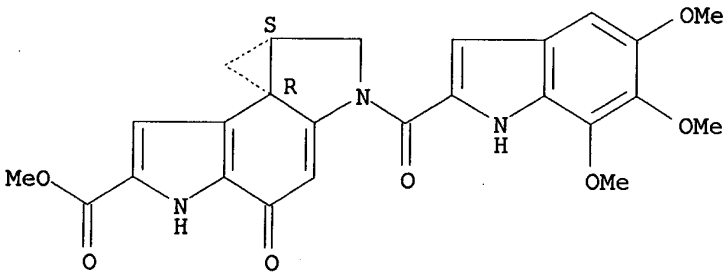


RN 118292-34-5 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,6,7,8,8a-octahydro-6-methyl-4,7-dioxo-2-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, methyl ester, (6R,7bR,8aS)- (9CI) (CA INDEX NAME)

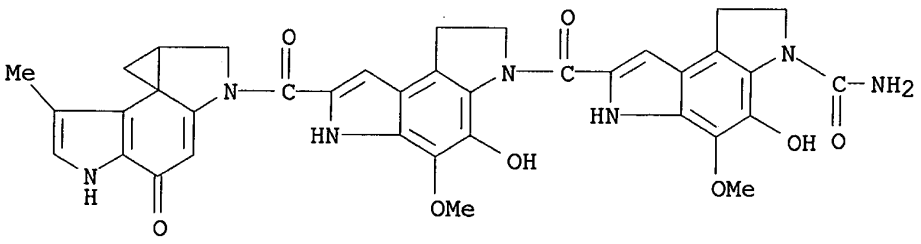


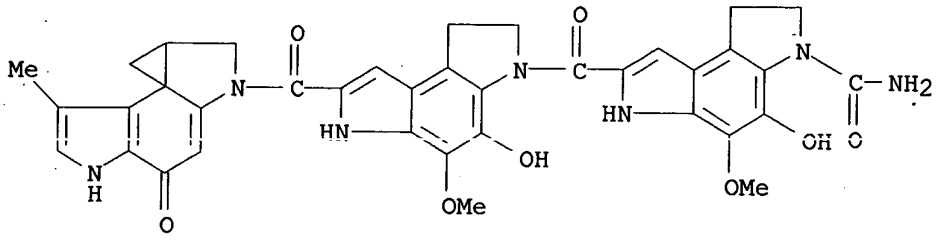
RN 130288-24-3 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,8,8a-hexahydro-4-oxo-2-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, methyl ester, (7bR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

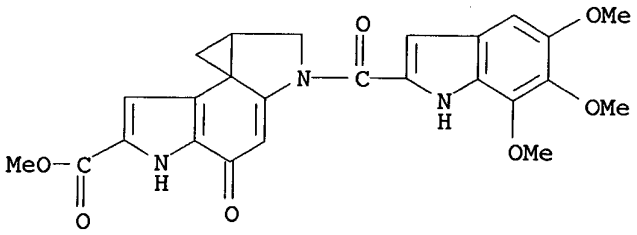


IT **110352-07-3P 151062-84-9P 160542-95-0P**
160637-26-3P 182957-16-0P 182957-17-1P
182957-18-2P 182957-19-3P 190060-29-8P
190060-30-1P 190060-31-2P 190060-32-3P
190060-33-4P 190060-41-4P 190060-45-8P
190060-46-9P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(duocarmycin SA shortened, simplified, and extended agents: a systematic examn. of the role of the **DNA** binding subunit)
RN 110352-07-3 HCAPLUS
CN Benzo[1,2-b:4,3-b']dipyrrole-3(2H)-carboxamide, 7-[[1,6-dihydro-4-hydroxy-5-methoxy-7-[[(7bS,8aR)-4,5,8,8a-tetrahydro-7-methyl-4-oxocyclopropa[c]pyrrolo[3,2-e]indol-2(1H)-yl]carbonyl]benzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-1,6-dihydro-4-hydroxy-5-methoxy- (9CI) (CA INDEX NAME)





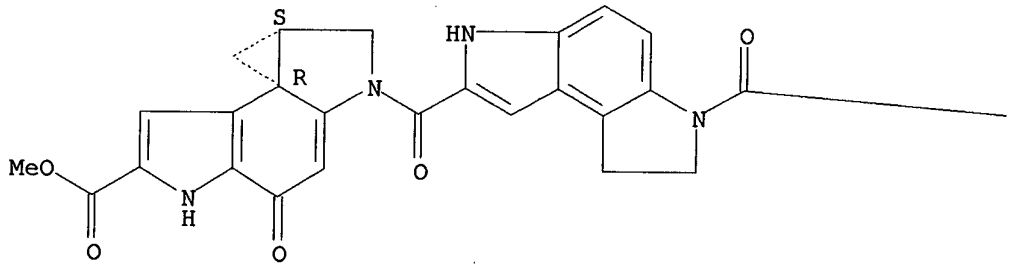
RN 151062-84-9 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,8,8a-hexahydro-4-oxo-2-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, methyl ester, (7bS,8aR)- (9CI) (CA INDEX NAME)



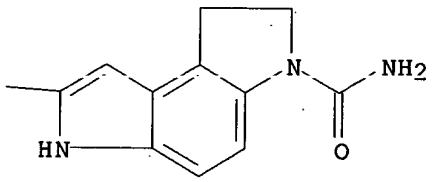
RN 160542-95-0 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 2-[[6-[[6-(aminocarbonyl)-3,6,7,8-tetrahydrobenzo[1,2-b:4,3-b']dipyrrol-2-yl]carbonyl]-3,6,7,8-tetrahydrobenzo[1,2-b:4,3-b']dipyrrol-2-yl]carbonyl]-1,2,4,5,8,8a-hexahydro-4-oxo-, methyl ester, (7bR,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

PAGE 1-A



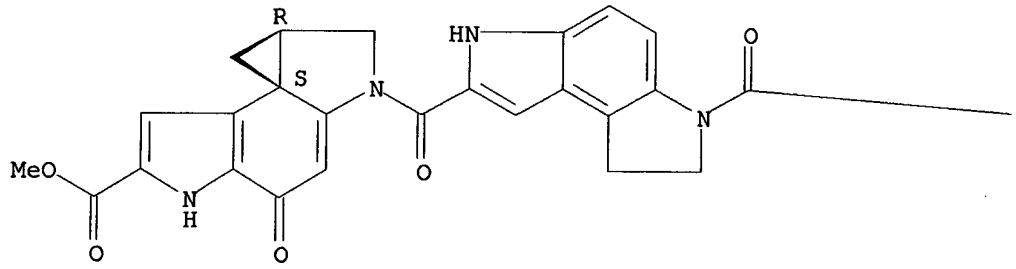
PAGE 1-B



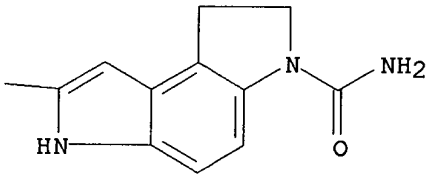
RN 160637-26-3 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 2-[[6-[[6-(aminocarbonyl)-3,6,7,8-tetrahydrobenzo[1,2-b:4,3-b']dipyrrol-2-yl]carbonyl]-3,6,7,8-tetrahydrobenzo[1,2-b:4,3-b']dipyrrol-2-yl]carbonyl]-1,2,4,5,8,8a-hexahydro-4-oxo-, methyl ester, (7bS,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

PAGE 1-A

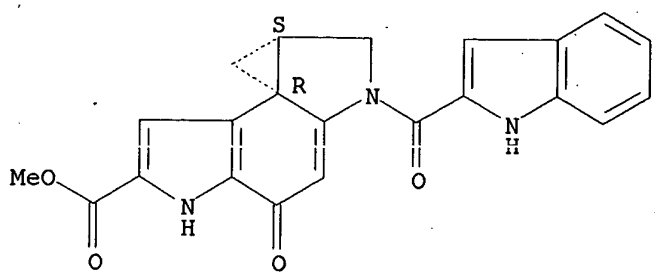


PAGE 1-B



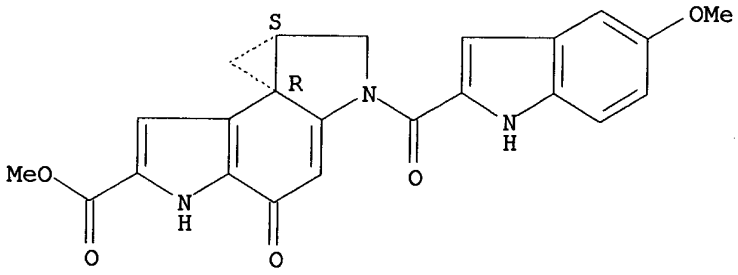
RN 182957-16-0 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,8,8a-hexahydro-2-(1H-indol-2-ylcarbonyl)-4-oxo-, methyl ester, (7bR,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



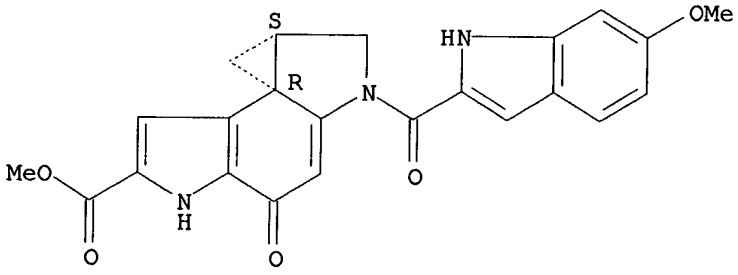
RN 182957-17-1 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,8,8a-hexahydro-2-[(5-methoxy-1H-indol-2-yl)carbonyl]-4-oxo-, methyl ester, (7bR,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



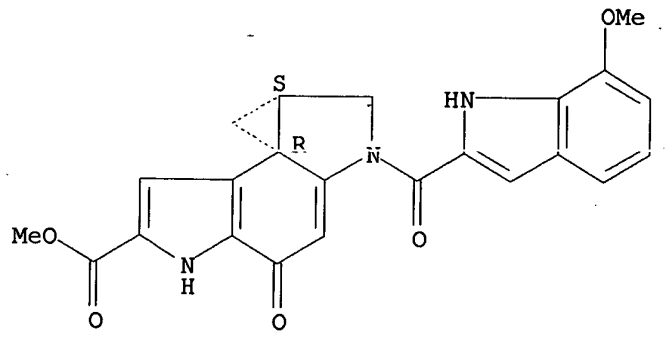
RN 182957-18-2 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,8,8a-hexahydro-2-[(6-methoxy-1H-indol-2-yl)carbonyl]-4-oxo-, methyl ester, (7bR,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



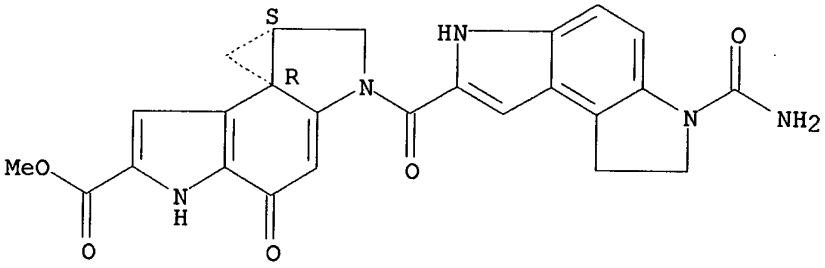
RN 182957-19-3 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,8,8a-hexahydro-2-[(7-methoxy-1H-indol-2-yl)carbonyl]-4-oxo-, methyl ester, (7bR,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



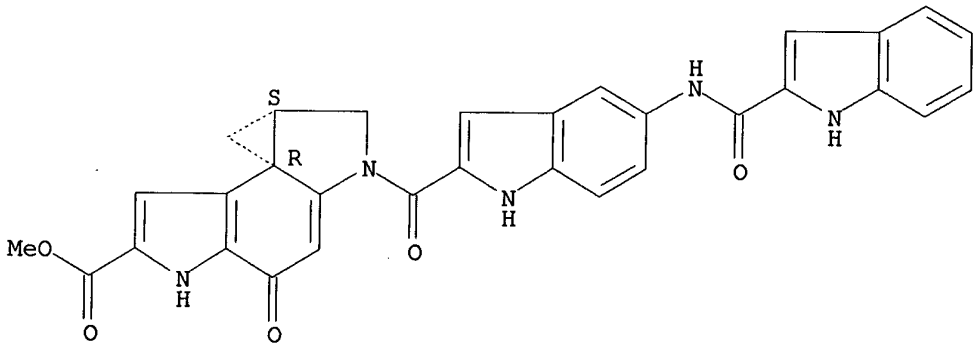
RN 190060-29-8 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 2-[[6-(aminocarbonyl)-3,6,7,8-tetrahydrobenzo[1,2-b:4,3-b']dipyrrol-2-yl]carbonyl]-1,2,4,5,8,8a-hexahydro-4-oxo-, methyl ester, (7bR,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 190060-30-1 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,8,8a-hexahydro-2-[[5-[(1H-indol-2-ylcarbonyl)amino]-1H-indol-2-yl]carbonyl]-4-oxo-, methyl ester, (7bR,8aS)- (9CI) (CA INDEX NAME)

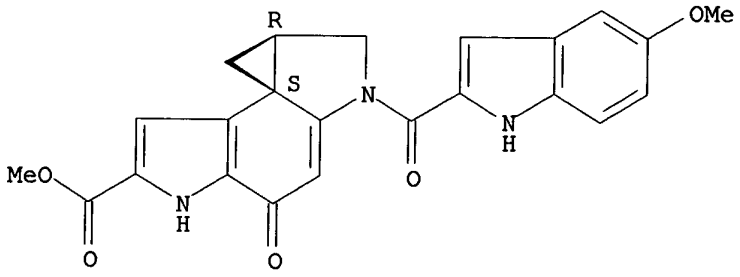
Absolute stereochemistry. Rotation (+).



RN 190060-31-2 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,8,8a-

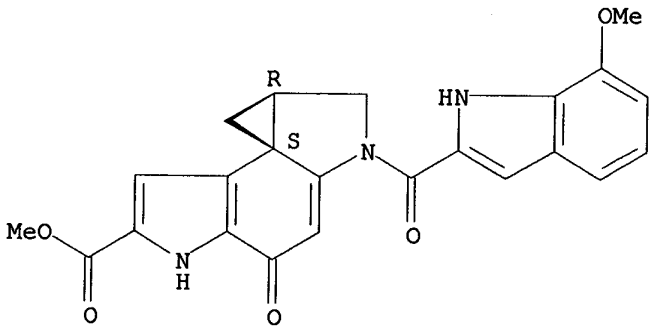
hexahydro-2-[(5-methoxy-1H-indol-2-yl)carbonyl]-4-oxo-, methyl ester, (7bS,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



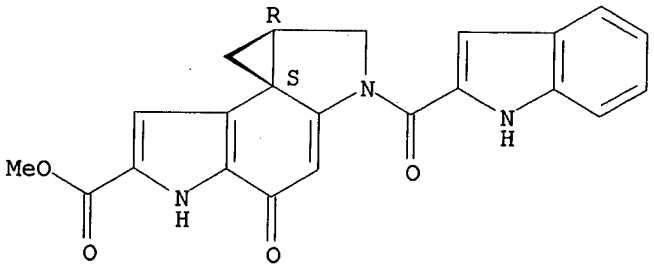
RN 190060-32-3 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,8,8a-hexahydro-2-[(7-methoxy-1H-indol-2-yl)carbonyl]-4-oxo-, methyl ester, (7bS,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



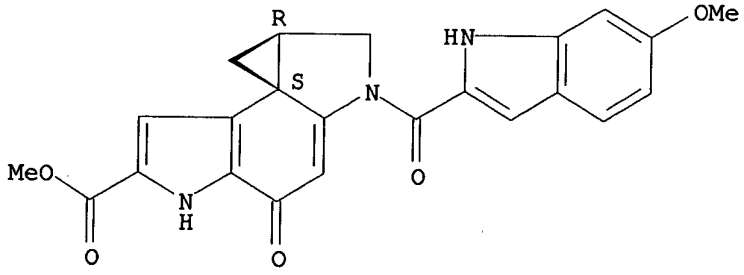
RN 190060-33-4 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,8,8a-hexahydro-2-(1H-indol-2-ylcarbonyl)-4-oxo-, methyl ester, (7bS,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



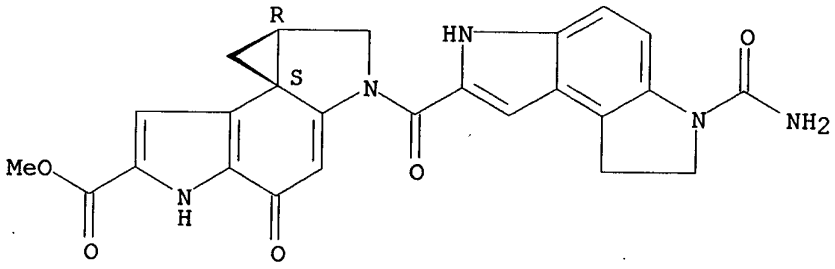
RN 190060-41-4 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,8,8a-hexahydro-2-[(6-methoxy-1H-indol-2-yl)carbonyl]-4-oxo-, methyl ester, (7bS,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



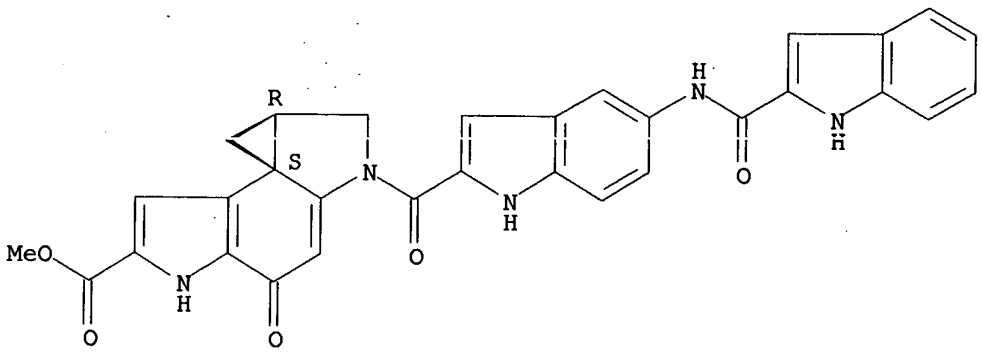
RN 190060-45-8 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 2-[[6-(aminocarbonyl)-3,6,7,8-tetrahydrobenzo[1,2-b:4,3-b']dipyrrol-2-yl]carbonyl]-1,2,4,5,8,8a-hexahydro-4-oxo-, methyl ester, (7bS,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 190060-46-9 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,8,8a-hexahydro-2-[[5-[(1H-indol-2-ylcarbonyl)amino]-1H-indol-2-yl]carbonyl]-4-oxo-, methyl ester, (7bS,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L37 ANSWER 13 OF 21 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1997:123321 HCAPLUS
DOCUMENT NUMBER: 126:207209
TITLE: pH dependence of the rate of DNA alkylation for (+)-duocarmycin SA and (+)-CCBI-TMI
AUTHOR(S): Boger, Dale L.; Boyce, Christopher W.; Johnson, Douglas S.
CORPORATE SOURCE: Department of Chemistry, The Scripps Research Institute, La Jolla, CA, 92037, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (1997), 7(2), 233-238
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A study of the DNA alkylation rate pH dependence with the establishment of pseudo first-order rate consts. for the title compds. at a single high affinity site in w794 DNA is detailed. This dependence proved to be remarkably small with the rates increasing only 1.89x and 2.5x, resp., over 2 pH units (pH 6-8).

CC 1-6 (Pharmacology)

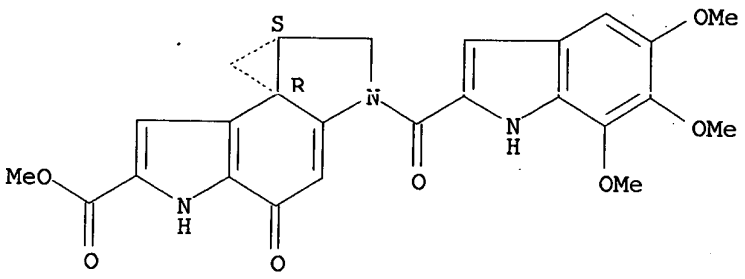
IT Alkylating agents, biological
Alkylation
pH
(pH dependence of rate of DNA alkylation for (+)-**duocarmycin** SA and (+)-CCBI-TMI)

IT **130288-24-3**, (+)-Duocarmycin SA **178962-98-6**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(pH dependence of rate of **DNA** alkylation for (+)-duocarmycin SA and (+)-CCBI-TMI)

IT **130288-24-3**, (+)-Duocarmycin SA **178962-98-6**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(pH dependence of rate of **DNA** alkylation for (+)-duocarmycin SA and (+)-CCBI-TMI)

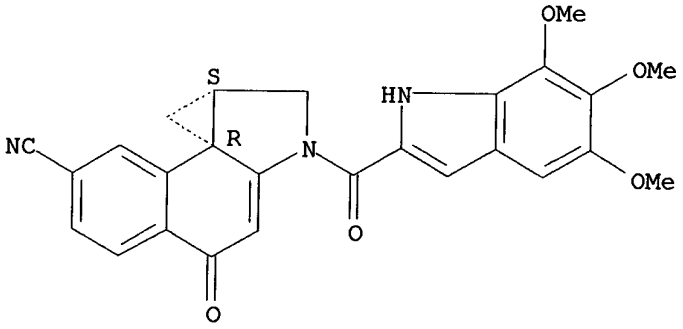
RN 130288-24-3 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,8,8a-hexahydro-4-oxo-2-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, methyl ester, (7bR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 178962-98-6 HCAPLUS
CN 1H-Benzo[e]cycloprop[c]indole-7-carbonitrile, 2,4,9,9a-tetrahydro-4-oxo-2-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, (8bR,9aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



L37 ANSWER 14 OF 21 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1996:746750 HCAPLUS
DOCUMENT NUMBER: 126:98920
TITLE: Distamycin A modulates the sequence specificity of DNA alkylation by duocarmycin A
AUTHOR(S): Sugiyama, Hiroshi; Lian, Chenyang; Isomura, Mariko; Saito, Isao; Wang, Andrew H.-J.
CORPORATE SOURCE: Dep. Synthetic Chem. Biol. Chem., Kyoto Univ., Kyoto, 606-01, Japan
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1996), 93(25), 14405-14410
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Duocarmycin A (Duo) normally alkylates adenine N3 at the 3' end of A+T-rich sequences in DNA. The efficient adenine alkylation by Duo is achieved by its monomeric binding to the DNA minor groove. The addn. of another minor groove binder, distamycin A (Dist), dramatically modulates the site of DNA alkylation by Duo, and the alkylation switches preferentially to G residues in G+C-rich sequences. HPLC product anal.

using oligonucleotides revealed a highly efficient G-N3 alkylation via the cooperative binding of a heterodimer between Duo and Dist to the minor groove. The three-dimensional structure of the ternary alkylated complex of Duo/Dist/d(CAGGTGGT).cntdot.d(ACCACCTG) has been detd. by nuclear Overhauser effect (NOE)-restrained refinement using 750 MHz two-dimensional NOE spectroscopy data. The refined NMR structure fully explains the sequence requirement of such modulated alkylations. This is the first demonstration of Duo DNA alkylation through cooperative binding with another structurally different natural product, and its suggests a promising new way to alter or modify the DNA alkylation selectivity in a predictable manner.

CC 1-6 (Pharmacology)

IT **Alkylation**
(biochem.; distamycin A modulates sequence specificity of DNA alkylation by **duocarmycin** A)

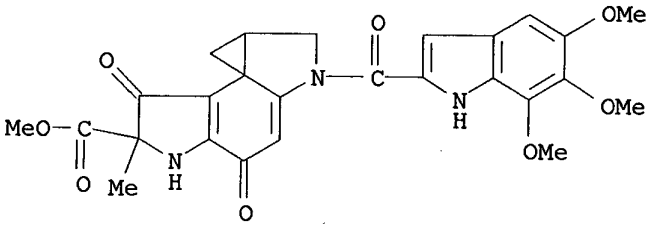
IT 636-47-5, Distamycin A **118292-34-5**, Duocarmycin A
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(distamycin A modulates sequence specificity of **DNA** alkylation by duocarmycin A)

IT **185947-54-0**
RL: BSU (Biological study, unclassified); MFM (Metabolic formation); PRP (Properties); BIOL (Biological study); FORM (Formation, nonpreparative)
(distamycin A modulates sequence specificity of **DNA** alkylation by duocarmycin A)

IT **118292-34-5**, Duocarmycin A
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(distamycin A modulates sequence specificity of **DNA** alkylation by duocarmycin A)

RN 118292-34-5 HCAPLUS

CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,6,7,8,8a-octahydro-6-methyl-4,7-dioxo-2-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, methyl ester, (6R,7bR,8aS)- (9CI) (CA INDEX NAME)



IT **185947-54-0**
RL: BSU (Biological study, unclassified); MFM (Metabolic formation); PRP (Properties); BIOL (Biological study); FORM (Formation, nonpreparative)
(distamycin A modulates sequence specificity of **DNA** alkylation by duocarmycin A)

RN 185947-54-0 HCAPLUS

CN Guanosine, 2'-deoxyadenylyl-(3'.fwdarw.5')-2'-deoxycytidylyl-(3'.fwdarw.5')-2'-deoxycytidylyl-(3'.fwdarw.5')-2'-deoxyadenylyl-(3'.fwdarw.5')-2'-deoxycytidylyl-(3'.fwdarw.5')-2'-deoxycytidylyl-(3'.fwdarw.5')-thymidylyl-(3'.fwdarw.5')-2'-deoxy-, double-stranded complementary, compd. with N-[5-[[(3-amino-3-iminopropyl)amino]carbonyl]-1-

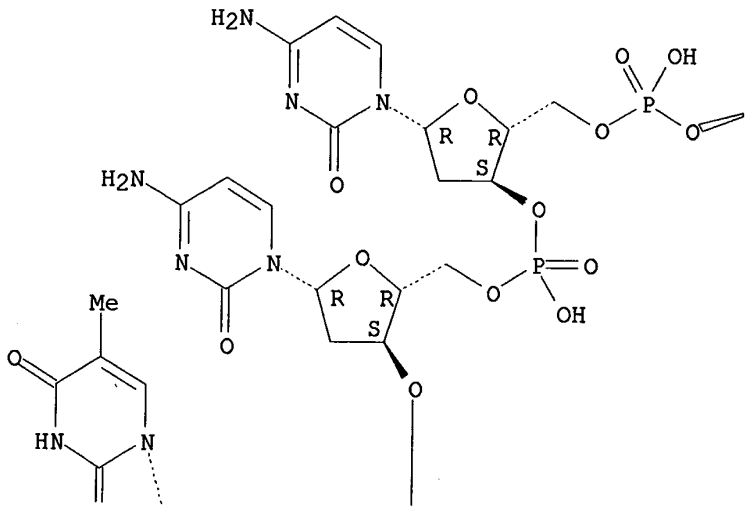
methyl-1H-pyrrol-3-yl]-4-[[[4-(formylamino)-1-methyl-1H-pyrrol-2-yl]carbonyl]amino]-1-methyl-1H-pyrrole-2-carboxamide and [6R-(6.alpha.,7bR*,8a.alpha.)]-methyl 1,2,4,5,6,7,8,8a-octahydro-6-methyl-4,7-dioxo-2-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylate (1:1:1) (9CI) (CA INDEX NAME)

CM 1

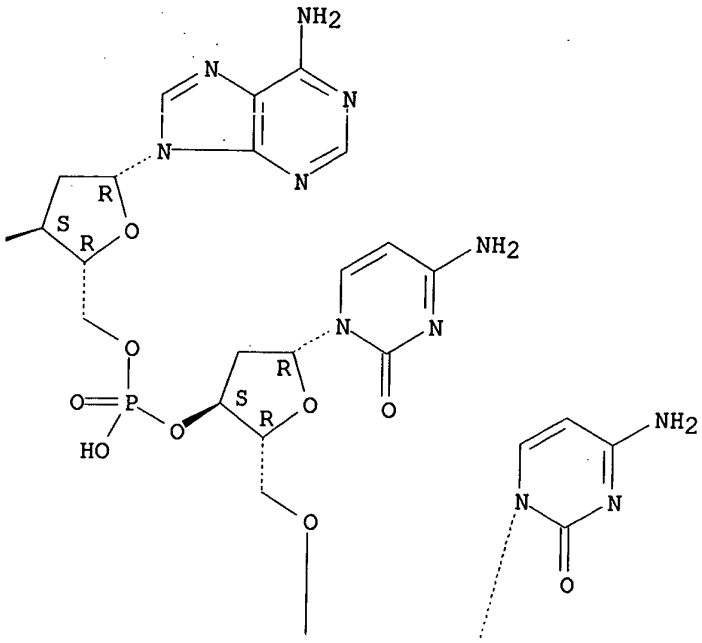
CRN 185947-51-7
CMF C76 H98 N29 O45 P7

Absolute stereochemistry.

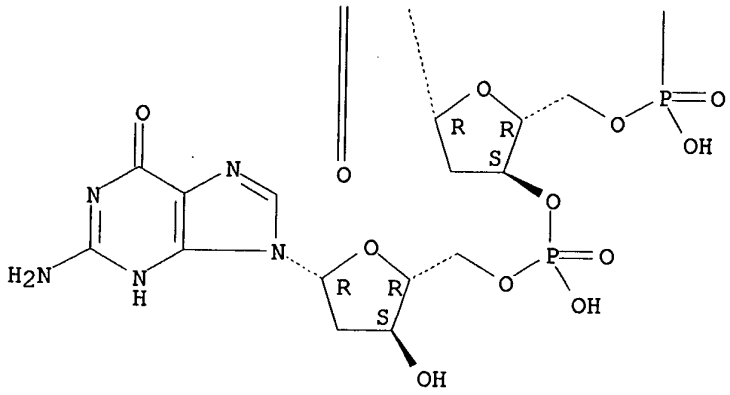
PAGE 1-A



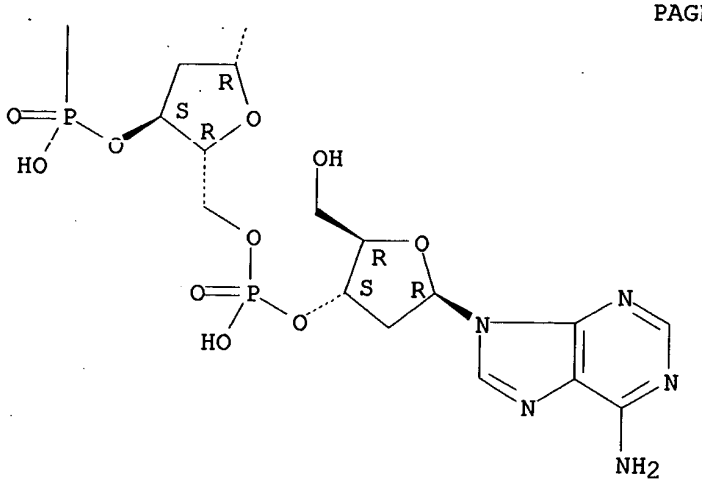
PAGE 1-B



PAGE 2-A



PAGE 2-B

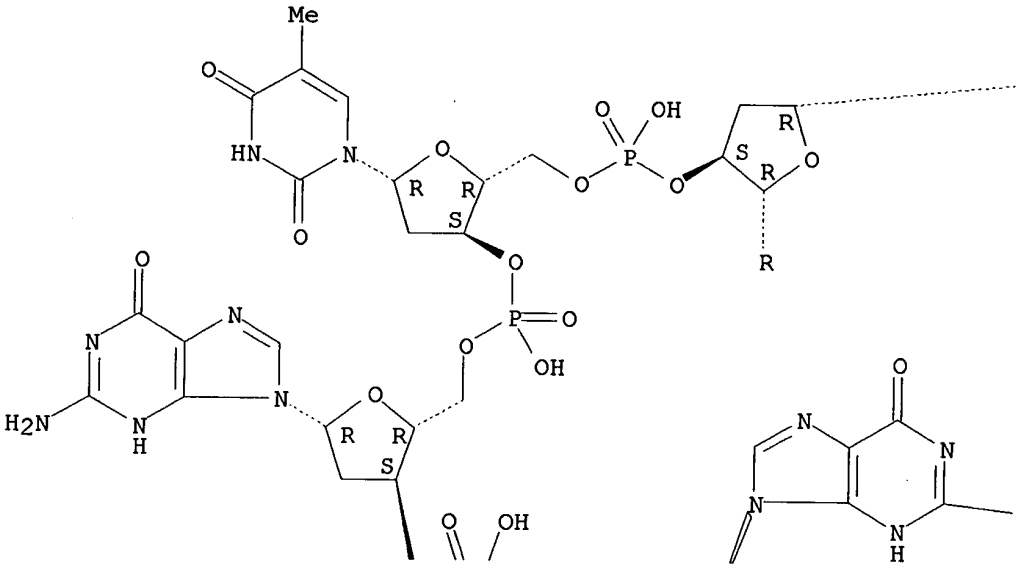


CM 2

CRN 185947-50-6
CMF C79 H99 N32 O47 P7

Absolute stereochemistry.

PAGE 1-A



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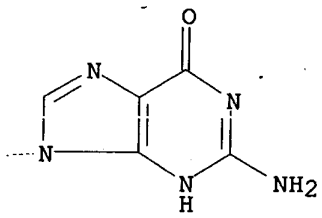
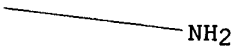
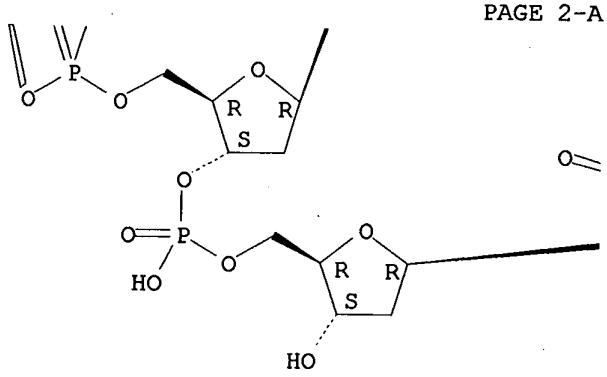
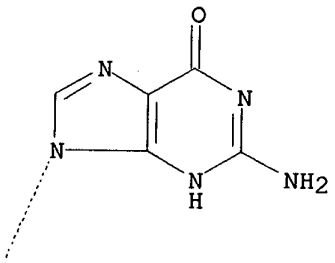


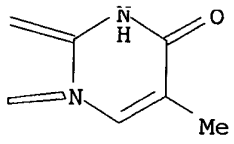


PAGE 2-A

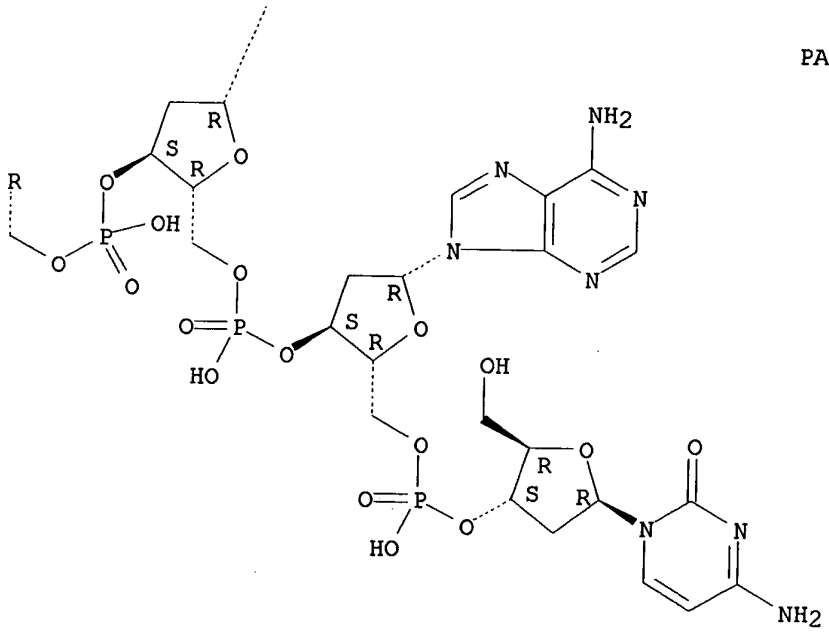




PAGE 2-B

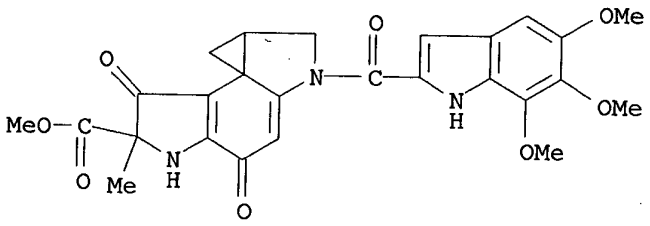


PAGE 3-A



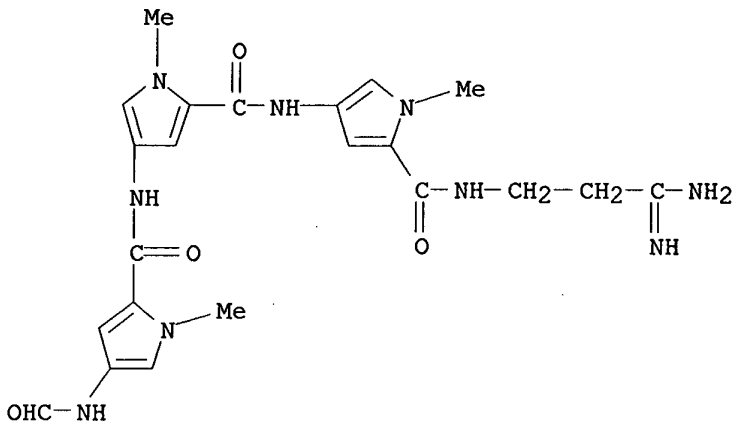
CM 3

CRN 118292-34-5
CMF C26 H25 N3 O8



CM 4

CRN 636-47-5
CMF C22 H27 N9 O4



L37 ANSWER 15 OF 21 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:315183 HCAPLUS
DOCUMENT NUMBER: 120:315183
TITLE: A Novel Property of Duocarmycin and Its Analogs for Covalent Reaction with DNA
AUTHOR(S): Asai, Akira; Nagamura, Satoru; Saito, HIromitsu
CORPORATE SOURCE: Tokyo Research Laboratories, Kyowa Hakko Kogyo Co. Ltd., Machida, 194, Japan
SOURCE: Journal of the American Chemical Society (1994), 116(10), 4171-7
CODEN: JACSAT; ISSN: 0002-7863
DOCUMENT TYPE: Journal
LANGUAGE: English

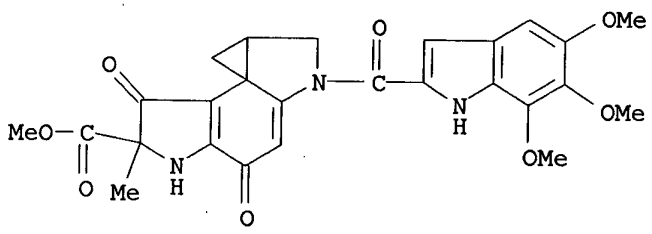
AB For understanding the mechanism of action of antitumor agents and designing new drugs, the DNA alkylating property of duocarmycin (DUM) and its analogs was examd. The thermal depurination products of calf thymus DNA covalently bonded to DUMA were revealed to be not only the DUMA-N3 adenine adduct but also unexpectedly the DUMA-N3 guanine adduct. In addn. DUMSA and 2 synthetic analogs with higher solvolytic stability, reacted more selectively with N3 adenine than DUMA did. The correlation between electrophilicity of the cyclopropanesubunit in the mol. and selectivity to adenine was obsd. KW-2189, a synthetic deriv. which has improved in vivo antitumor activity, was designed as a prodrug requiring enzymic hydrolysis of the carbamoyl moiety, followed by the drug regeneration. Surprisingly the authors discovered that KW-2189 itself alkylated DNA covalently without release of the carbamoyl moiety. For the mechanism of DNA alkylation by KW-2189, a novel alkylating reaction via the formation of an iminium intermediate without loss of the carbamoyl moiety was proposed.

CC 1-3 (Pharmacology)
IT **Alkylation**
(of DNA, by **duocarmycin** analogs, structure effect on)
IT **118292-34-5**, Duocarmycin A **118292-34-5D**, Duocarmycin A, analogs 118292-35-6 118292-36-7 124325-93-5 124325-94-6 **130288-24-3 153925-97-4 153925-98-5**

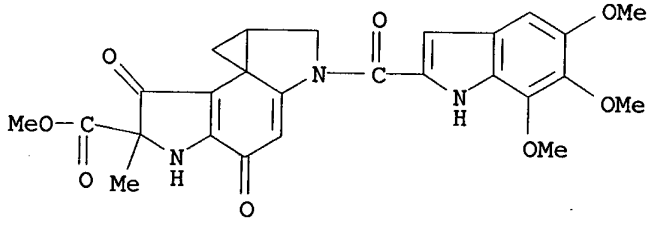
154889-68-6, KW 2189
RL: PRP (Properties)
(**DNA** alkylating property of, structure effect on)

IT **118292-34-5**, Duocarmycin A **118292-34-5D**, Duocarmycin A, analogs **130288-24-3 153925-97-4 153925-98-5**
RL: PRP (Properties)
(**DNA** alkylating property of, structure effect on)

RN 118292-34-5 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,6,7,8,8a-octahydro-6-methyl-4,7-dioxo-2-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, methyl ester, (6R,7bR,8aS)- (9CI) (CA INDEX NAME)

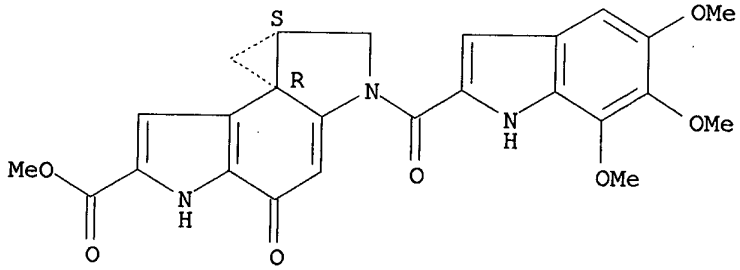


RN 118292-34-5 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,6,7,8,8a-octahydro-6-methyl-4,7-dioxo-2-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, methyl ester, (6R,7bR,8aS)- (9CI) (CA INDEX NAME)



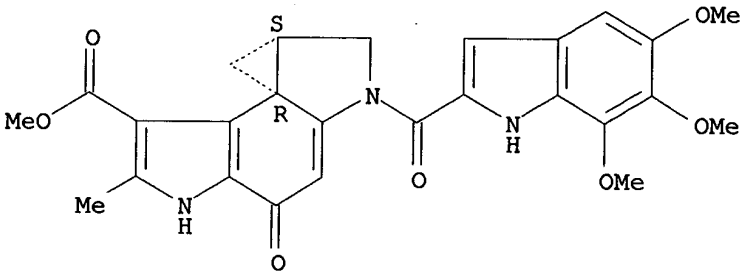
RN 130288-24-3 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,8,8a-hexahydro-4-oxo-2-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, methyl ester, (7bR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



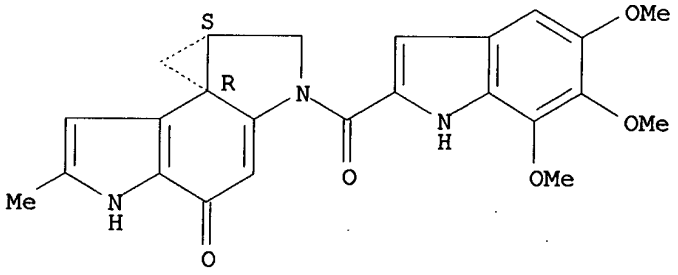
RN 153925-97-4 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-7-carboxylic acid, 1,2,4,5,8,8a-hexahydro-6-methyl-4-oxo-2-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, methyl ester, (7bR,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 153925-98-5 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indol-4(5H)-one, 1,2,8,8a-tetrahydro-6-methyl-2-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, (7bR,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L37 ANSWER 16 OF 21 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1994:153162 HCAPLUS
DOCUMENT NUMBER: 120:153162
TITLE: (+)- and ent-(-)-Duocarmycin SA and (+)- and ent-(-)-N-BOC-DSA DNA Alkylation Properties.Alkylation Site Models That Accommodate the Offset AT-Rich Adenine N3 Alkylation Selectivity of the Enantiomeric Agents
AUTHOR(S): Boger, Dale L.; Johnson, Douglas S.; Yun, Weiya
CORPORATE SOURCE: Department of Chemistry, The Scripps Research Institute, La Jolla, CA, 92037, USA
SOURCE: Journal of the American Chemical Society (1994), 116(5), 1635-56
CODEN: JACSAT; ISSN: 0002-7863
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A detailed study of the DNA alkylation properties of (+)-duocarmycin SA, ent-(-)-duocarmycin SA, and (+)- and ent-(-)-N-BOC-DSA is described, and

the development of a model that accommodates the offset AT-rich adenine N3 alkylation selectivity of the enantiomeric agents is presented.

CC 1-6 (Pharmacology)

IT **Alkylation**
(of DNA, by **duocarmycin** and BOC DSA enantiomers, mol. model of)

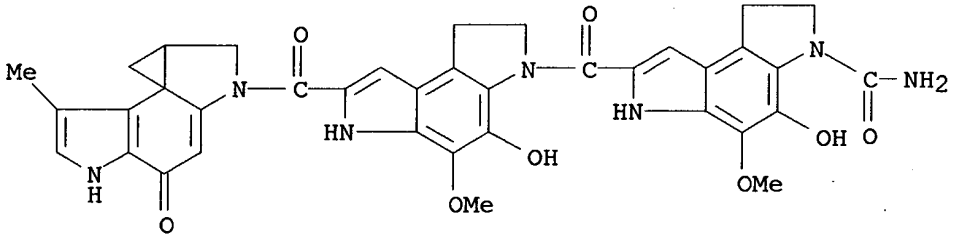
IT **69866-21-3,** (+)-CC-1065 **118292-34-5 127232-82-0 127306-33-6 128050-92-0 128050-93-1 128300-14-1 128300-16-3 149405-55-0**
RL: RCT (Reactant); RACT (Reactant or reagent)
(**DNA** alkylation by)

IT **130288-24-3,** (+)-Duocarmycin SA 144732-53-6 **151062-84-9**, ent-(-)-Duocarmycin SA 151062-86-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(**DNA** alkylation by, mol. model of)

IT **69866-21-3,** (+)-CC-1065 **118292-34-5 127232-82-0 127306-33-6 128050-92-0 128050-93-1 128300-14-1 128300-16-3 149405-55-0**
RL: RCT (Reactant); RACT (Reactant or reagent)
(**DNA** alkylation by)

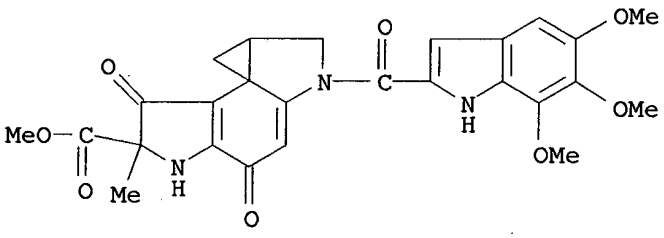
RN 69866-21-3 HCAPLUS

CN Benzo[1,2-b:4,3-b']dipyrrole-3(2H)-carboxamide, 7-[[1,6-dihydro-4-hydroxy-5-methoxy-7-[(4,5,8,8a-tetrahydro-7-methyl-4-oxocyclopropa[c]pyrrolo[3,2-e]indol-2(1H)-yl)carbonyl]benzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-1,6-dihydro-4-hydroxy-5-methoxy-, (7bR,8aS)- (9CI) (CA INDEX NAME)



RN 118292-34-5 HCAPLUS

CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,6,7,8,8a-octahydro-6-methyl-4,7-dioxo-2-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, methyl ester, (6R,7bR,8aS)- (9CI) (CA INDEX NAME)

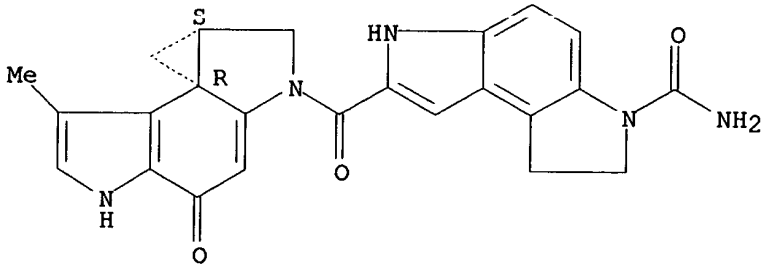


RN 127232-82-0 HCAPLUS

CN Benzo[1,2-b:4,3-b']dipyrrole-3(2H)-carboxamide, 1,6-dihydro-7-[(4,5,8,8a-tetrahydro-7-methyl-4-oxocyclopropa[c]pyrrolo[3,2-e]indol-2(1H)-

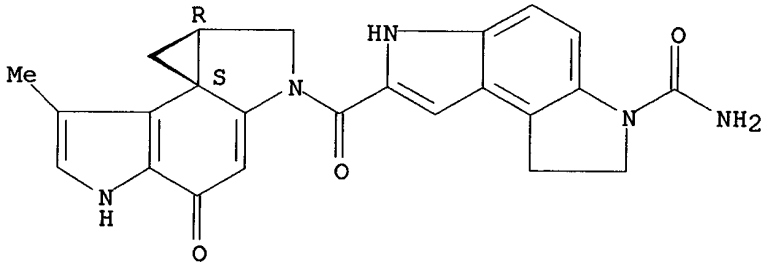
yl)carbonyl]-, (7bR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

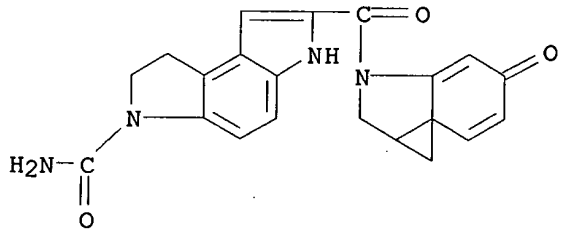


RN 127306-33-6 HCAPLUS
CN Benzo[1,2-b:4,3-b']dipyrrole-3(2H)-carboxamide, 1,6-dihydro-7-[(4,5,8,8a-tetrahydro-7-methyl-4-oxocyclopropa[c]pyrrolo[3,2-e]indol-2(1H)-yl)carbonyl]-, (7bS)- (9CI) (CA INDEX NAME)

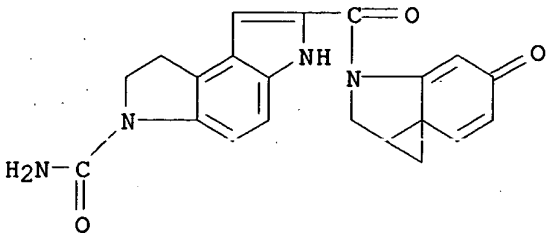
Absolute stereochemistry. Rotation (-).



RN 128050-92-0 HCAPLUS
CN Benzo[1,2-b:4,3-b']dipyrrole-3(2H)-carboxamide, 7-[(1a,2-dihydro-5-oxo-1H-cycloprop[c]indol-3(5H)-yl)carbonyl]-1,6-dihydro-, (1aR)- (9CI) (CA INDEX NAME)

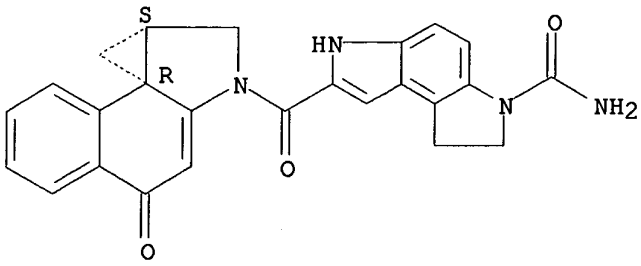


RN 128050-93-1 HCAPLUS
CN Benzo[1,2-b:4,3-b']dipyrrole-3(2H)-carboxamide, 7-[(1a,2-dihydro-5-oxo-1H-cycloprop[c]indol-3(5H)-yl)carbonyl]-1,6-dihydro-, (1aS)- (9CI) (CA INDEX NAME)



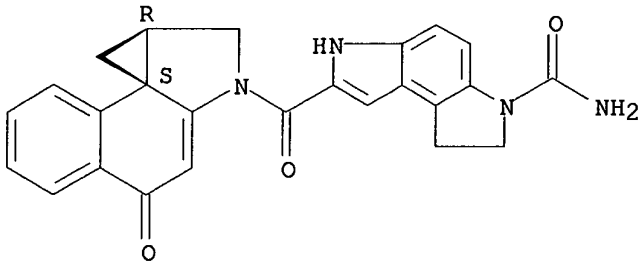
RN 128300-14-1 HCAPLUS
CN Benzo[1,2-b:4,3-b']dipyrrole-3(2H)-carboxamide, 7-[[(8bR,9aS)-9,9a-dihydro-4-oxo-1H-benzo[e]cycloprop[c]indol-2(4H)-yl]carbonyl]-1,6-dihydro- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



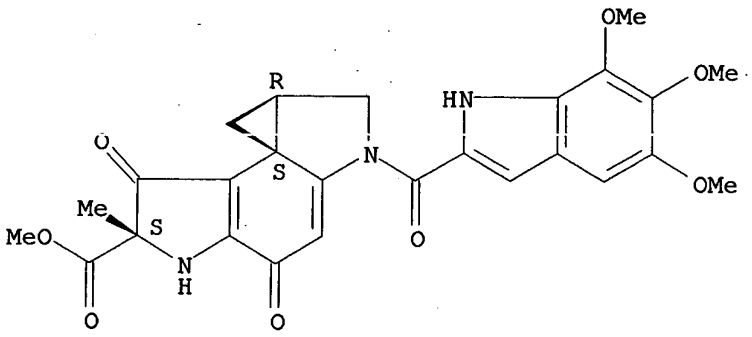
RN 128300-16-3 HCAPLUS
CN Benzo[1,2-b:4,3-b']dipyrrole-3(2H)-carboxamide, 7-[(9,9a-dihydro-4-oxo-1H-benzo[e]cycloprop[c]indol-2(4H)-yl)carbonyl]-1,6-dihydro-, (8bS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



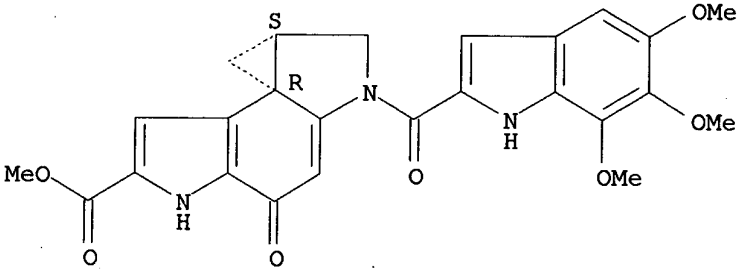
RN 149405-55-0 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,6,7,8,8a-octahydro-6-methyl-4,7-dioxo-2-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, methyl ester, (6S,7bS,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

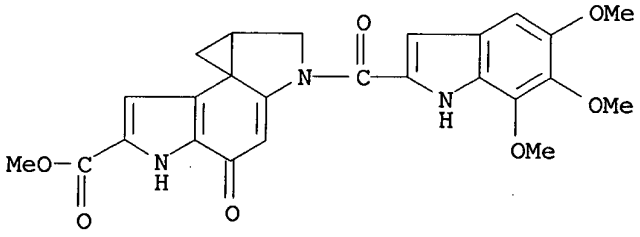


IT **130288-24-3,** (+)-Duocarmycin SA **151062-84-9,** ent-(-)-Duocarmycin SA
RL: RCT (Reactant); RACT (Reactant or reagent)
(**DNA** alkylation by, mol. model of)
RN 130288-24-3 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,8,8a-hexahydro-4-oxo-2-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, methyl ester, (7bR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 151062-84-9 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,8,8a-hexahydro-4-oxo-2-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, methyl ester, (7bS,8aR)- (9CI) (CA INDEX NAME)



L37 ANSWER 17 OF 21 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1993:649752 HCAPLUS

DOCUMENT NUMBER: 119:249752
TITLE: Reversibility of the duocarmycin A and SA DNA alkylation reaction
AUTHOR(S): Boger, Dale L.; Yun, Weiya
CORPORATE SOURCE: Dep. Chem., Scripps Res. Inst., La Jolla, CA, 92037, USA
SOURCE: Journal of the American Chemical Society (1993), 115(21), 9872-3
CODEN: JACSAT; ISSN: 0002-7863
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The alkylation of duplex w794 DNA by the title compds., unlike that of (+)-CC-1065, was demonstrated to be a reversible reaction. The relationship to the cytotoxicity of these compds. is discussed.

CC 26-6 (Biomolecules and Their Synthetic Analogs)
Section cross-reference(s): 6

IT **Alkylation**
(of DNA by **duocarmycins**, reversibility of)

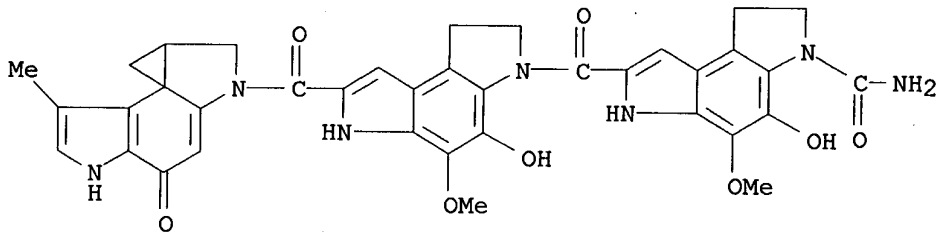
IT **69866-21-3**, (+)-CC-1065
RL: RCT (Reactant); RACT (Reactant or reagent)
(**DNA** alkylation by)

IT **118292-34-5 130288-24-3**
RL: RCT (Reactant); RACT (Reactant or reagent)
(**DNA** alkylation by, reversibility of)

IT **69866-21-3**, (+)-CC-1065
RL: RCT (Reactant); RACT (Reactant or reagent)
(**DNA** alkylation by)

RN 69866-21-3 HCAPLUS

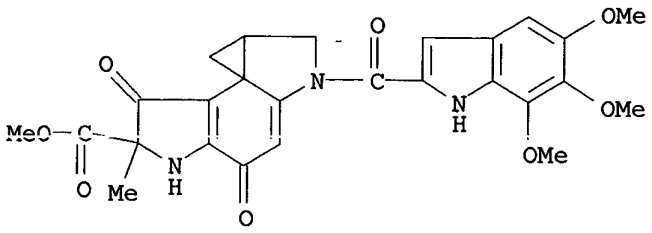
CN Benzo[1,2-b:4,3-b']dipyrrole-3(2H)-carboxamide, 7-[[1,6-dihydro-4-hydroxy-5-methoxy-7-[(4,5,8,8a-tetrahydro-7-methyl-4-oxocyclopropa[c]pyrrolo[3,2-e]indol-2(1H)-yl)carbonyl]benzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-1,6-dihydro-4-hydroxy-5-methoxy-, (7bR,8aS)- (9CI) (CA INDEX NAME)



IT **118292-34-5 130288-24-3**
RL: RCT (Reactant); RACT (Reactant or reagent)
(**DNA** alkylation by, reversibility of)

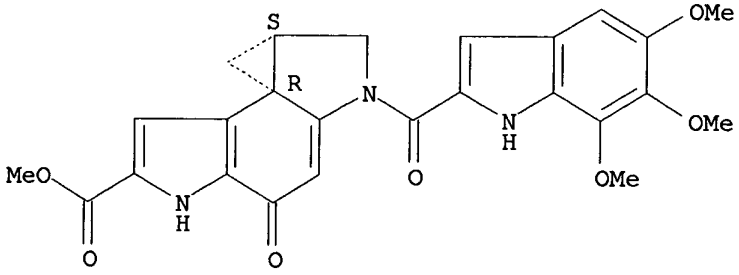
RN 118292-34-5 HCAPLUS

CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,6,7,8,8a-octahydro-6-methyl-4,7-dioxo-2-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, methyl ester, (6R,7bR,8aS)- (9CI) (CA INDEX NAME)



RN 130288-24-3 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,8,8a-hexahydro-4-oxo-2-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, methyl ester, (7bR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

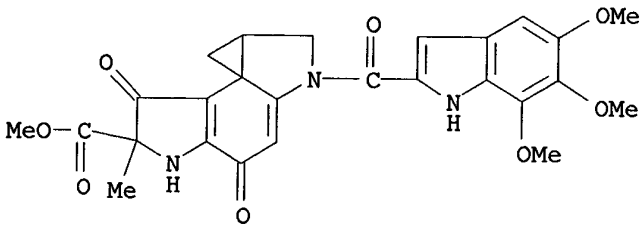


L37 ANSWER 18 OF 21 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1993:616823 HCAPLUS
DOCUMENT NUMBER: 119:216823
TITLE: DNA alkylation properties of the duocarmycins: (+)-duocarmycin A, epi-(+)-duocarmycin A, ent-(-)-duocarmycin A and epi,ent-(-)-duocarmycin A
AUTHOR(S): Boger, Dale L.; Yun, Weiya; Terashima, Shiro; Fukuda, Yasumichi; Nakatani, Kazuhiko; Kitos, Paul A.; Jin, Qing
CORPORATE SOURCE: Dep. Chem., Scripps Res. Inst., La Jolla, CA, 92037, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (1992), 2(7), 759-65
CODEN: BMCLE8; ISSN: 0960-894X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The comparative in vitro cytotoxic activity and DNA-alkylating properties of both enantiomers of the 2 diastereomers of (+)-duocarmycin A are detailed. The DNA-alkylating efficiency and in vitro cytotoxic potency of the natural enantiomers ((+)-duocarmycin A > epi-(+)-duocarmycin A) exceeded those of the unnatural enantiomers (ent-(-)-duocarmycin A, epi,ent-(-)-duocarmycin A) by .gtoreq.100-fold.
CC 1-6 (Pharmacology)
IT **Alkylation**
(of DNA by **duocarmycin** A diastereomers)
IT **118292-34-5 149405-55-0 149405-58-3 149405-59-4**

RL: BIOL (Biological study)
(cytotoxic and **DNA**-alkylating properties of)

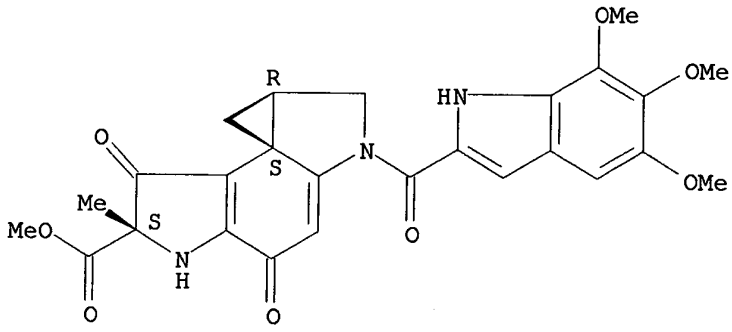
IT **118292-34-5 149405-55-0 149405-58-3**
149405-59-4
RL: BIOL (Biological study)
(cytotoxic and **DNA**-alkylating properties of)

RN 118292-34-5 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,6,7,8,8a-octahydro-6-methyl-4,7-dioxo-2-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, methyl ester, (6R,7bR,8aS)- (9CI) (CA INDEX NAME)



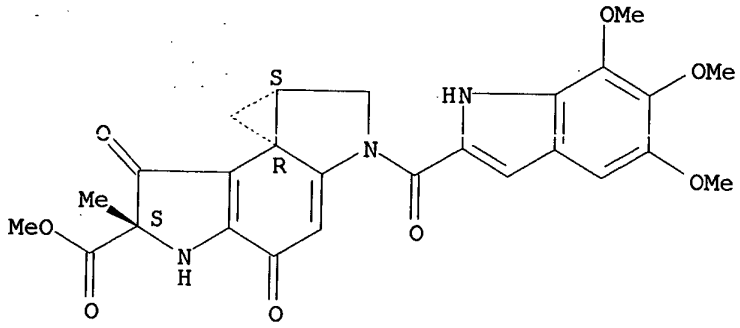
RN 149405-55-0 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,6,7,8,8a-octahydro-6-methyl-4,7-dioxo-2-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, methyl ester, (6S,7bS,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



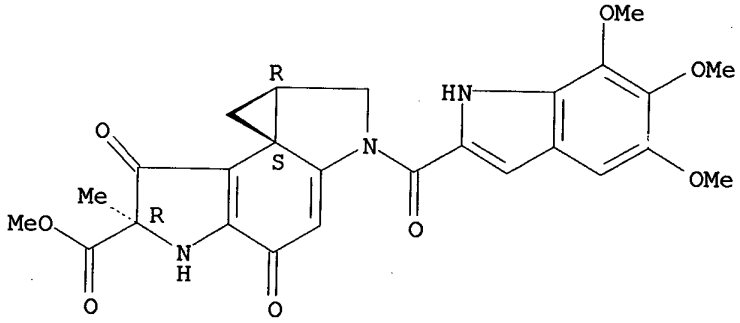
RN 149405-58-3 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,6,7,8,8a-octahydro-6-methyl-4,7-dioxo-2-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, methyl ester, (6S,7bR,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 149405-59-4 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,6,7,8,8a-octahydro-6-methyl-4,7-dioxo-2-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, methyl ester, (6R,7bS,8aR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



L37 ANSWER 19 OF 21 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1992:503427 HCAPLUS
DOCUMENT NUMBER: 117:103427
TITLE: Highly stereospecific reactions in DNA duplex
AUTHOR(S): Saito, Isao; Sugiyama, Hiroshi
CORPORATE SOURCE: Fac. Eng., Kyoto Univ., Kyoto, 606, Japan
SOURCE: Yuki Gosei Kagaku Kenkyusho Koenshu (1992), 6, 87-93
CODEN: YGKKEI; ISSN: 0913-8463
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese

AB A review, with 3 refs., on the stereospecific reaction of DNA duplex contg. a cyclopentane moiety with bleomycin and on the stereospecific alkylation of DNA the duplex with duacarmycin A and kapurimycin A3.

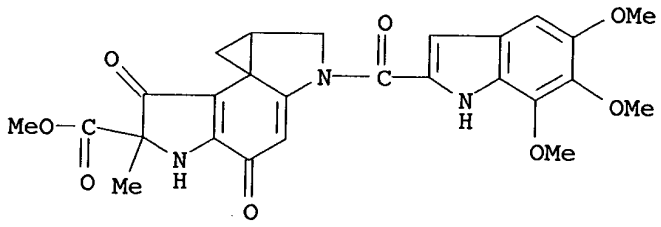
CC 1-0 (Pharmacology)

IT **Alkylation**
(biochem., of DNA duplex reaction products with bleomycin, by **duocarmycin** A and kapurimycin A3)

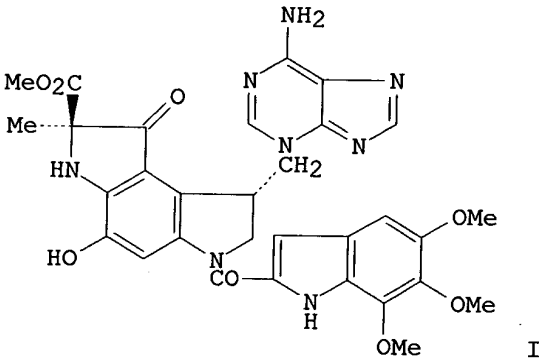
IT **118292-34-5**, Duocarmycin A 129966-45-6, Kapurimycin A3
RL: RCT (Reactant); RACT (Reactant or reagent)
(**DNA** duplex reaction products with bleomycin alkylation by)

IT **118292-34-5**, Duocarmycin A

RL: RCT (Reactant); RACT (Reactant or reagent)
(**DNA** duplex reaction products with bleomycin alkylation by)
RN 118292-34-5 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,6,7,8,8a-octahydro-6-methyl-4,7-dioxo-2-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, methyl ester, (6R,7bR,8aS)- (9CI) (CA INDEX NAME)



L37 ANSWER 20 OF 21 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1991:484929 HCAPLUS
DOCUMENT NUMBER: 115:84929
TITLE: Isolation and characterization of the duocarmycin-adenine DNA adduct
AUTHOR(S): Boger, Dale L.; Ishizaki, Takayoshi; Zarrinmayeh, Hamideh
CORPORATE SOURCE: Dep. Chem., Purdue Univ., West Lafayette, IN, 47907, USA
SOURCE: Journal of the American Chemical Society (1991), 113(17), 6645-9
CODEN: JACSAT; ISSN: 0002-7863
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB Duocarmycin-adenine adduct (I) was isolated following alkylation of calf thymus DNA with duocarmycin. I was fully characterized by using 1H-NMR, 2D 1H-1H COSY NMR, 2D 1H-1H NOESY NMR, and 13C-NMR. The data provided unambiguous assignment of the structure I in which adenine N-3 addn. to the unsubstituted cyclopropane C of duocarmycin A was established.

CC 1-6 (Pharmacology)

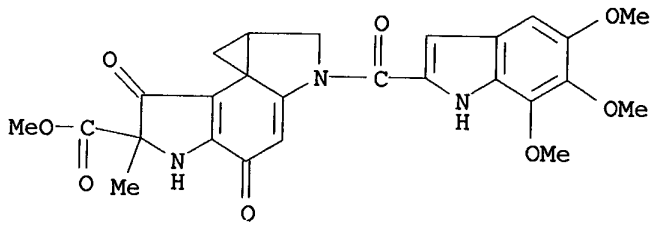
IT **Alkylation**
(biochem., of DNA, by **duocarmycin**, adenine adduct formation in)

IT **118292-34-5**, Duocarmycin A 118292-35-6, Duocarmycin C1 118292-36-7, Duocarmycin C2 124325-93-5, Duocarmycin B1 124325-94-6, Duocarmycin B2 **130288-24-3**, Duocarmycin SA
RL: BIOL (Biological study)
(**DNA** alkylation by, adenine adduct formation in)

IT **118292-34-5**, Duocarmycin A **130288-24-3**, Duocarmycin SA
RL: BIOL (Biological study)
(**DNA** alkylation by, adenine adduct formation in)

RN 118292-34-5 HCAPLUS

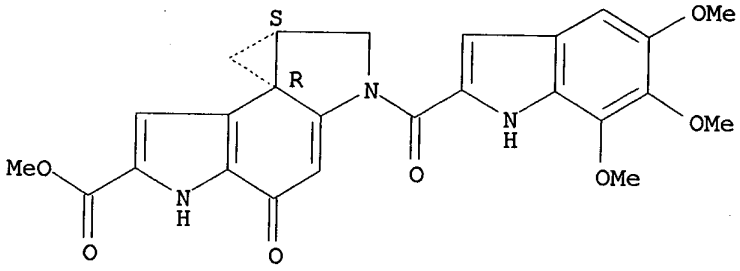
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,6,7,8,8a-octahydro-6-methyl-4,7-dioxo-2-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, methyl ester, (6R,7bR,8aS)- (9CI) (CA INDEX NAME)



RN 130288-24-3 HCAPLUS

CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,8,8a-hexahydro-4-oxo-2-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, methyl ester, (7bR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L37 ANSWER 21 OF 21 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 1991:23617 HCAPLUS

DOCUMENT NUMBER: 114:23617

TITLE: Duocarmycin-pyrindamycin DNA alkylation properties and identification, synthesis, and evaluation of agents incorporating the pharmacophore of the duocarmycin-pyrindamycin alkylation subunit. Identification of the CC-1065 duocarmycin common pharmacophore

AUTHOR(S): Boger, Dale L.; Ishizaki, Takayoshi; Zarrinmayeh, Hamideh; Munk, Stephen A.; Kitos, Paul A.; Suntornwat, Oranart
CORPORATE SOURCE: Dep. Chem., Purdue Univ., West Lafayette, IN, 47907, USA
SOURCE: Journal of the American Chemical Society (1990), 112(24), 8961-71
CODEN: JACSAT; ISSN: 0002-7863
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 114:23617
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB A demonstration and subsequent study of the DNA covalent alkylation properties of duocarmycin A (I) and duocarmycins C1 and C2 [pyrindamycin A (II) and B (III)] are detailed and have led to the identification of two high affinity binding sites [5'-d(A/TAAA)-3 and 5'-d(A/TTTAPu)-3'] within a full set of available alkylation sites [5'-d(AAA)-3' > 5'-d(TTA)-3' > 5'-d(TAA)-3' > 5'-d(ATA)-3'] that proceeds through 3'-adenine N-3 alkylation of the activated cyclopropane of I similar to the (+)-CC-1065 covalent alkylation of DNA. The synthesis of ketone IV (CI-TMI) incorporating the parent 1,2,7,7a-tetrahydrocycloprop[1,2-c]indol-4-one (CI) alkylation subunit of I is described and the results of its comparative evaluation (in vitro cytotoxic activity and DNA covalent alkylation properties) suggest that IV constitutes an agent bearing the min. potent pharmacophore of DNA alkylation subunit of I and the common pharmacophore of the I/ML-1065 alkylation subunits.

CC 26-6 (Biomolecules and Their Synthetic Analogs)
Section cross-reference(s): 33

IT **Alkylation**
(of DNA by **duocarmycin** related compds., binding site for)

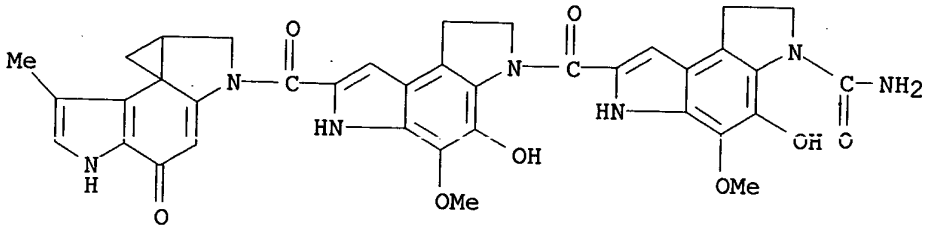
IT **69866-21-3**, CC-1065 **118292-34-5**, Duocarmycin A
118292-35-6, Pyrindamycin B 118292-36-7, Pyrindamycin A 130469-60-2
130469-61-3
RL: RCT (Reactant); RACT (Reactant or reagent)
(alkylation by, of **DNA**, binding sites for)

IT **128781-10-2P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn., hydrochlorination-ring opening, and alkylation by, of **DNA**)

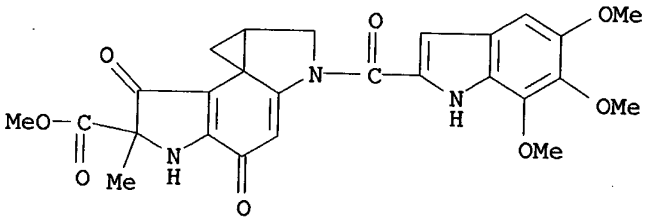
IT **69866-21-3**, CC-1065 **118292-34-5**, Duocarmycin A
RL: RCT (Reactant); RACT (Reactant or reagent)
(alkylation by, of **DNA**, binding sites for)

RN 69866-21-3 HCAPLUS

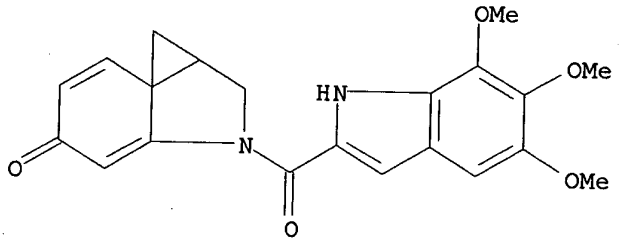
CN Benzo[1,2-b:4,3-b']dipyrrole-3(2H)-carboxamide, 7-[[1,6-dihydro-4-hydroxy-5-methoxy-7-[(4,5,8,8a-tetrahydro-7-methyl-4-oxocyclopropa[c]pyrrolo[3,2-e]indol-2(1H)-yl)carbonyl]benzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-1,6-dihydro-4-hydroxy-5-methoxy-, (7bR,8aS)- (9CI) (CA INDEX NAME)



RN 118292-34-5 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-6-carboxylic acid, 1,2,4,5,6,7,8,8a-octahydro-6-methyl-4,7-dioxo-2-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]-, methyl ester, (6R,7bR,8aS)- (9CI) (CA INDEX NAME)



IT **128781-10-2P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn., hydrochlorination-ring opening, and alkylation by, of **DNA**)
RN 128781-10-2 HCAPLUS
CN 5H-Cycloprop[c]indol-5-one, 1,1a,2,3-tetrahydro-3-[(5,6,7-trimethoxy-1H-indol-2-yl)carbonyl]- (9CI) (CA INDEX NAME)



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L12       42238 SEA FILE=REGISTRY ABB=ON  PLU=ON  L11 AND C3/ESS
L13             STR

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DEFAULT ECLEVEL IS LIMITED
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ECOUNT  IS M3 C  AT   3

GRAPH ATTRIBUTES:
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NUMBER OF NODES IS   4

STEREO ATTRIBUTES: NONE
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L25         153 SEA FILE=HCAPLUS ABB=ON  PLU=ON  MICROTITRATION+OLD/CT
L26         613 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L15 AND (DNA OR RNA OR
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L31           2 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L26 AND ((L24 OR L25) OR
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=> d ibib abs hitind hitstr l31 1-2

L31  ANSWER 1 OF 2  HCAPLUS  COPYRIGHT 2003 ACS
ACCESSION NUMBER:         2001:365880  HCAPLUS
DOCUMENT NUMBER:          134:366795
TITLE:                    DNA sequence recognition by
                          pyrrole-imidazole polyamide for use in anticancer drug
                          screening
INVENTOR(S):              Sugiyama, Hiroshi; Saito, Akira; Iida, Hirokazu
PATENT ASSIGNEE(S):       Foundation for Scientific Technology Promotion, Japan
SOURCE:                   Jpn. Kokai Tokkyo Koho, 14 pp.
                          CODEN: JKXXAF
DOCUMENT TYPE:            Patent
LANGUAGE:                 Japanese
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE          APPLICATION NO.  DATE
     ---------------   ----  --------      ---------------  --------
     JP 2001136974      A2   20010522      JP 1999-326007   19991116
     WO 2001036677      A1   20010525      WO 2000-JP7992   20001113
         W:  US
         RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL,
             PT, SE, TR
     EP 1152061         A1   20011107      EP 2000-974961   20001113
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
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IE, FI
US 2003099998 A1 20030529 US 2002-285030 20021101
PRIORITY APPLN. INFO.: JP 1999-326007 A 19991116
WO 2000-JP7992 W 20001113
US 2001-889379 A3 20010716

AB Novel chem. species represented by the following general formula B-L-A (B = a chem. structure capable of recognizing the base sequence of **DNA**, for example, optionally substituted pyrrole-imidazole polyamide; A = a chem. structure capable of binding to unnatural nucleotide bases, for example, the alkylation moiety of duocarmycin A; L = a linker capable of binding the chem. structures A and B, for example, vinyl) and use of those compds. in screening of biol. activity of chem. compds. are disclosed. Those compds. are preferably **DNA** alkylating agents, applicable as anticancer agents. Reagent kits for screening, including microtiter plates, are claimed. Drug screening using human cancer cell lines, CL-wt cells, HLC-2 cells, Jurkat cells, and HeLa cells, and synthetic scheme for the bioactive compds., are described.

IC ICM C12N015-09
ICS C12M001-26; C12Q001-68; C07D487-04

CC 27-10 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1

ST **DNA** sequence recognition duocarmycin pyrrole imidazole polyamide conjugate; pyrrole imidazole polyamide **DNA** alkylating agent anticancer drug screening

IT Animal cell line
(CL-wt, drug screening in; **DNA** sequence recognition by pyrrole-imidazole polyamide for use in anticancer drug screening)

IT Alkylating agents, biological
Antitumor agents
Drug screening
Microtiter plates
(**DNA** sequence recognition by pyrrole-imidazole polyamide for use in anticancer drug screening)

IT Polyamides, properties
RL: ARU (Analytical role, unclassified); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); PRP (Properties); ANST (Analytical study); BIOL (Biological study); PROC (Process); USES (Uses)
(**DNA** sequence recognition by pyrrole-imidazole polyamide for use in anticancer drug screening)

IT Animal cell line
(HLC-2, drug screening in; **DNA** sequence recognition by pyrrole-imidazole polyamide for use in anticancer drug screening)

IT Animal cell line
(JURKAT, drug screening in; **DNA** sequence recognition by pyrrole-imidazole polyamide for use in anticancer drug screening)

IT HeLa cell
(drug screening in; **DNA** sequence recognition by pyrrole-imidazole polyamide for use in anticancer drug screening)

IT Test kits
(for drug screening; **DNA** sequence recognition by pyrrole-imidazole polyamide for use in anticancer drug screening)

IT 109-97-7D, Pyrrole, deriv. 288-32-4D, Imidazole, deriv.
339984-88-2 339984-91-7
RL: ARU (Analytical role, unclassified); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological

study, unclassified); BUU (Biological use, unclassified); PRP (Properties); ANST (Analytical study); BIOL (Biological study); PROC (Process); USES (Uses)
(**DNA** sequence recognition by pyrrole-imidazole polyamide for use in anticancer drug screening)

IT **339984-92-8P**
RL: ARU (Analytical role, unclassified); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); PRP (Properties); SPN (Synthetic preparation); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(**DNA** sequence recognition by pyrrole-imidazole polyamide for use in anticancer drug screening)

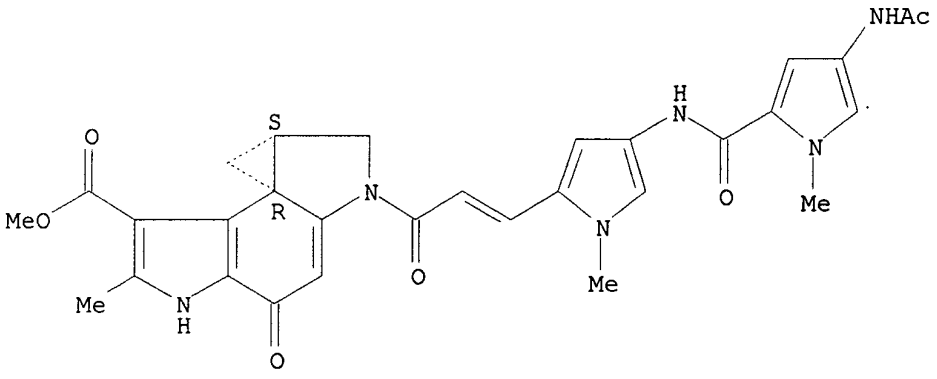
IT 1192-58-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(**DNA** sequence recognition by pyrrole-imidazole polyamide for use in anticancer drug screening)

IT 18711-27-8P, 1-Methyl-4-nitro-pyrrole-2-carboxy aldehyde 339984-93-9P 339984-94-0P, Bis-pyrrole 339984-95-1P, Tris-pyrrole 339984-96-2DP, imidazole ester
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(**DNA** sequence recognition by pyrrole-imidazole polyamide for use in anticancer drug screening)

IT **339984-88-2 339984-91-7**
RL: ARU (Analytical role, unclassified); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); PRP (Properties); ANST (Analytical study); BIOL (Biological study); PROC (Process); USES (Uses)
(**DNA** sequence recognition by pyrrole-imidazole polyamide for use in anticancer drug screening)

RN 339984-88-2 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-7-carboxylic acid, 2-[3-[4-[[[4-(acetylamino)-1-methyl-1H-pyrrol-2-yl]carbonyl]amino]-1-methyl-1H-pyrrol-2-yl]-1-oxo-2-propenyl]-1,2,4,5,8,8a-hexahydro-6-methyl-4-oxo-, methyl ester, (7bR,8aS)- (9CI) (CA INDEX NAME)

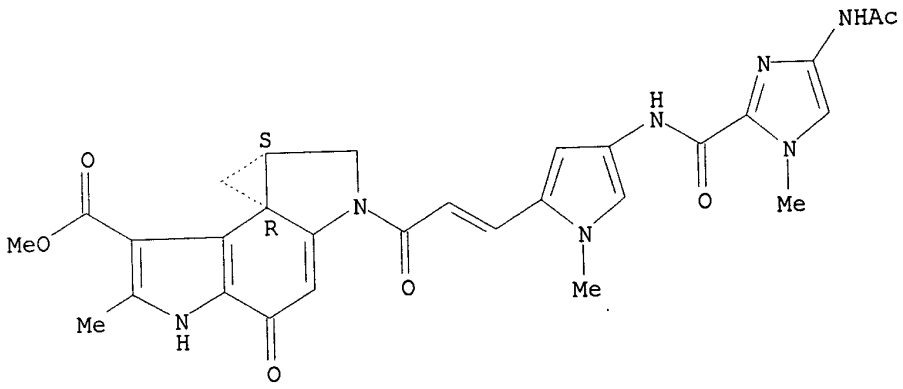
Absolute stereochemistry.
Double bond geometry unknown.



RN 339984-91-7 HCAPLUS

CN Cyclopropa[c]pyrrolo[3,2-e]indole-7-carboxylic acid, 2-[3-[4-[[[4-(acetylamino)-1-methyl-1H-imidazol-2-yl]carbonyl]amino]-1-methyl-1H-pyrrol-2-yl]-1-oxo-2-propenyl]-1,2,4,5,8,8a-hexahydro-6-methyl-4-oxo-, methyl ester, (7bR,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



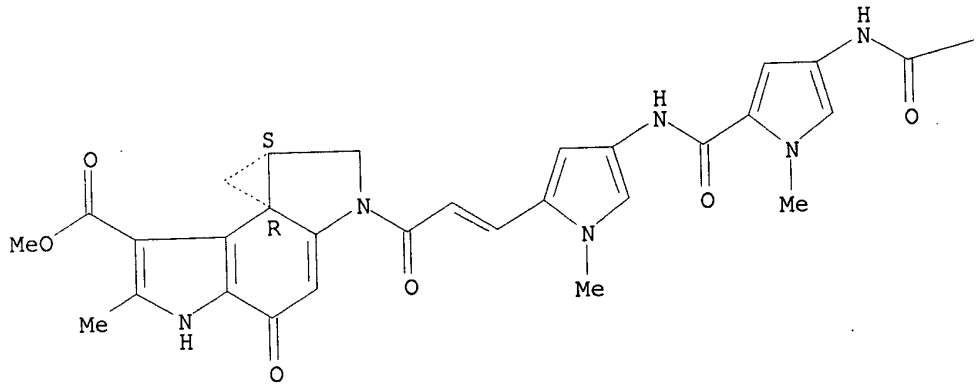
IT **339984-92-8P**
RL: ARU (Analytical role, unclassified); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); PRP (Properties); SPN (Synthetic preparation); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(**DNA** sequence recognition by pyrrole-imidazole polyamide for use in anticancer drug screening)

RN 339984-92-8 HCAPLUS

CN Cyclopropa[c]pyrrolo[3,2-e]indole-7-carboxylic acid, 2-[3-[4-[[[4-[[[4-(acetylamino)-1-methyl-1H-pyrrol-2-yl]carbonyl]amino]-1-methyl-1H-pyrrol-2-yl]carbonyl]amino]-1-methyl-1H-pyrrol-2-yl]-1-oxo-2-propenyl]-1,2,4,5,8,8a-hexahydro-6-methyl-4-oxo-, methyl ester, (7bR,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

PAGE 1-A



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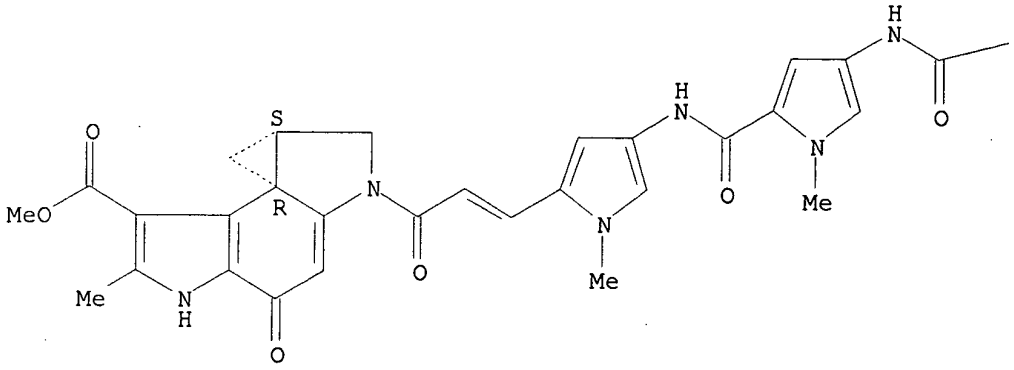

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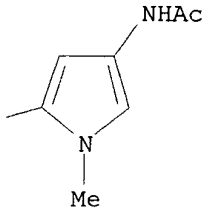


L31 ANSWER 2 OF 2 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:756909 HCAPLUS
DOCUMENT NUMBER: 133:317531
TITLE: Nematodes for screening of compounds with potential pharmacological activity
INVENTOR(S): Verwaerde, Philippe; Platteeuw, Christ; Cuvillier, Gwladys; Bogaert, Thierry
PATENT ASSIGNEE(S): Devgen N.V., Belg.
SOURCE: PCT Int. Appl., 137 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000063427	A2	20001026	WO 2000-IB575	20000414
WO 2000063427	A3	20011206		

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG,

SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW,
AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE,
DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF,
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

GB 2351151	A1	20001220	GB 2000-9358	20000414
GB 2359358	A1	20010822	GB 2001-11712	20000414
GB 2359358	B2	20020327		
GB 2359359	A1	20010822	GB 2001-11713	20000414
GB 2359359	B2	20020123		
GB 2359360	A1	20010822	GB 2001-11783	20000414
GB 2359360	B2	20020116		
GB 2359361	A1	20010822	GB 2001-11787	20000414
GB 2359361	B2	20020116		
GB 2359626	A1	20010829	GB 2001-11714	20000414
GB 2359626	B2	20020501		
GB 2359627	A1	20010829	GB 2001-11778	20000414
GB 2359627	B2	20020123		
EP 1175506	A2	20020130	EP 2000-920972	20000414
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002542466	T2	20021210	JP 2000-612504	20000414
HK 1030047	A1	20011102	HK 2001-100427	20010117

PRIORITY APPLN. INFO.:

GB 1999-8670	A	19990415
US 1999-129596P	P	19990415
GB 2000-9358	A3	20000414
WO 2000-IB575	W	20000414

AB Screening methods are provided which use nematode worms, particularly but not exclusively Caenorhabditis elegans , which are adapted to be performed in a high-throughput format.

IC ICM C12Q001-02
ICS C12Q001-18; C12Q001-68

CC 1-1 (Pharmacology)

IT Sensors
(**multi-well plate** reader; nematodes for screening of compds. with potential pharmacol. activity)

IT Diglycerides
Gene
Neurotransmitters
Nucleic acids
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(nematodes for screening of compds. with potential pharmacol. activity)

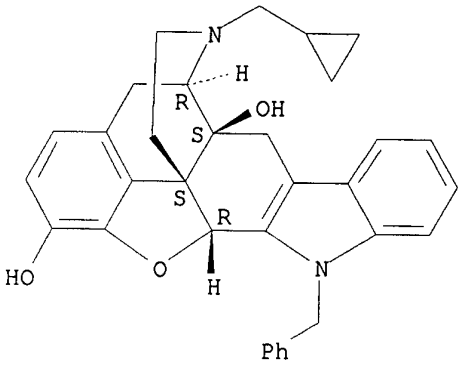
IT 51-55-8, Atropine, biological studies 52-52-8, Cycloleucine 52-68-6, Metrifonate 57-41-0, Diphenylhydantoin 57-47-6, Physostigmine 60-57-1, Dieldrin 83-79-4, Rotenone 101-31-5, L-Hyoscyamine 124-87-8, Picrotoxin 303-49-1, Clomipramine 407-41-0, O-Phospho-L-serine 882-09-7, Clofibric acid 1225-56-5, Nordoxepin 1477-50-5, Indole-2-carboxylic acid 1668-19-5, Doxepin 2062-78-4, Pimozide 3040-38-8 3054-07-7, DL-2-Aminosuberic acid 4910-46-7, Spaglumic acid 10540-29-1, Tamoxifen 19216-56-9, Prazosin 20862-11-7, N-Desisopropylpropranolol 21655-84-5, Harmane hydrochloride 23052-80-4, L-AP3 23052-81-5, L-AP4 24219-97-4, Mianserin 33978-72-2, YS-035 36112-95-5, Propranolol glycol 54910-89-3, Fluoxetine 65277-42-1, Ketoconazole 68506-86-5, Vigabatrin 70288-86-7, Ivermectin 78594-87-3, ZAPA 79055-67-7 79055-68-8, D-AP5 82900-57-0, BP554 93379-54-5, S-(-)-Atenolol 111872-98-1

112830-95-2, HU 210 119630-76-1 121050-04-2 133052-90-1, GF 109203X
140924-22-7 142326-59-8, L-701324 **155512-37-1**
169505-93-5, RS 17053 170984-70-0 182485-36-5 185259-85-2,
GR 46611 302897-18-3, GBLD 345
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(nematodes for screening of compds. with potential pharmacol. activity)

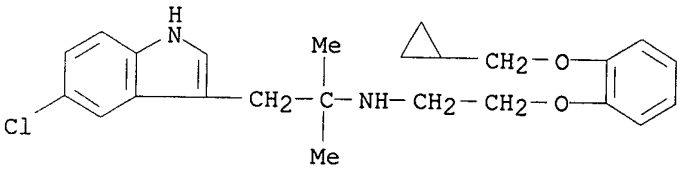
IT **155512-37-1 169505-93-5**, RS 17053
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(nematodes for screening of compds. with potential pharmacol. activity)

RN 155512-37-1 HCAPLUS
CN 4,8-Methanobenzofuro[2,3-a]pyrido[4,3-b]carbazole-1,8a(9H)-diol, 7-(cyclopropylmethyl)-5,6,7,8,14,14b-hexahydro-14-(phenylmethyl)-, (4bS,8R,8aS,14bR)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 169505-93-5 HCAPLUS
CN 1H-Indole-3-ethanamine, 5-chloro-N-[2-[2-(cyclopropylmethoxy)phenoxy]ethyl]-.alpha.,.alpha.-dimethyl-, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

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L12        42238 SEA FILE=REGISTRY ABB=ON  PLU=ON  L11 AND C3/ESS
L13             STR

Hy~G2~Cy        A @4
 1   2   3

REP G2=(1-10) 4
NODE ATTRIBUTES:
NSPEC   IS RC     AT   4
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED
ECOUNT  IS M3 C  M1 N  AT   1
ECOUNT  IS M3 C  AT   3

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS   4

STEREO ATTRIBUTES: NONE
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L29        73191 SEA FILE=HCAPLUS ABB=ON  PLU=ON  POLYAMIDES/CT
L30            8 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L26 AND L29


=> d ibib abs hitind hitstr 1-8 l30

L30  ANSWER 1 OF 8  HCAPLUS  COPYRIGHT 2003 ACS
ACCESSION NUMBER:         2003:348783  HCAPLUS
DOCUMENT NUMBER:          138:363789
TITLE:                    Polyamide-alkylator conjugates for selective
                          alkylation of double-stranded DNA
INVENTOR(S):              Dervan, Peter B.; Wurtz, Nicholas; Chang, Aileen
PATENT ASSIGNEE(S):       California Institute of Technology, USA
SOURCE:                   U.S., 52 pp.
                          CODEN: USXXAM
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE          APPLICATION NO.  DATE
     ---------------   ----  --------      ---------------  --------
     US 6559125         B1   20030506      US 2001-772315   20010126
PRIORITY APPLN. INFO.:                    US 2000-178821P  P 20000128
AB   Pyrrole- and/or imidazole-contg. polyamides conjugated with DNA
     alkylating agents are disclosed. These conjugates bind selectively to
     double-stranded DNA and alkylates one of the two strands. Thus,
     chlorambucil was attached to the .gamma.-aminobutyric acid moiety of an
     eight-ring polyamide targeting the HIV promoter. This conjugate bound
     with subnanomolar affinity and selectively alkylated the DNA.
     Addnl., polyamide conjugates with the two stereoisomers of
     1-(chloromethyl)-5-hydroxy-1,2-dihydro-3H-benz[e]indole were prepd. The
```

conjugates with opposite stereochem. provide opposite strand reactivity in the minor grove of the dsDNA.

IC ICM A61K038-00
ICS A01N043-04; C12Q001-68; C07H021-00

NCL 514012000; 514002000; 514044000; 435006000; 536023100; 536024300; 536025300

CC 3-1 (Biochemical Genetics)

IT Alkylating agents, biological
(conjugates; polyamide-alkylator conjugates for selective alkylation of double-stranded **DNA**)

IT **Polyamides, biological studies**
RL: BUU (Biological use, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); USES (Uses)
(conjugates; polyamide-alkylator conjugates for selective alkylation of double-stranded **DNA**)

IT **DNA**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(double-stranded; polyamide-alkylator conjugates for selective alkylation of double-stranded **DNA**)

IT Chloramines
RL: BUU (Biological use, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); USES (Uses)
(nitrogen mustards, conjugates; polyamide-alkylator conjugates for selective alkylation of double-stranded **DNA**)

IT Alkylation
(of **DNA**; polyamide-alkylator conjugates for selective alkylation of double-stranded **DNA**)

IT 305-03-3DP, Chlorambucil, polyamide conjugates 1404-00-8DP, Mitomycin, polyamide conjugates **69866-21-3DP**, (+)-CC-1065, polyamide conjugates 199806-31-0DP, polyamide conjugates 269402-52-0P 287719-58-8P 287719-59-9P
RL: BUU (Biological use, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); USES (Uses)
(polyamide-alkylator conjugates for selective alkylation of double-stranded **DNA**)

IT 109-55-7, 3-(Dimethylamino)propylamine 3303-84-2, Boc-.beta.-alanine 79642-50-5, Disuccinimidyl glutarate 130007-86-2 130008-89-8 287719-60-2 287719-61-3 287719-62-4 287719-63-5
RL: RCT (Reactant); RACT (Reactant or reagent)
(polyamide-alkylator conjugates for selective alkylation of double-stranded **DNA**)

IT 269402-55-3P 287719-54-4P 287719-55-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(polyamide-alkylator conjugates for selective alkylation of double-stranded **DNA**)

IT 269402-54-2P
RL: SPN (Synthetic preparation); PREP (Preparation)
(polyamide-alkylator conjugates for selective alkylation of double-stranded **DNA**)

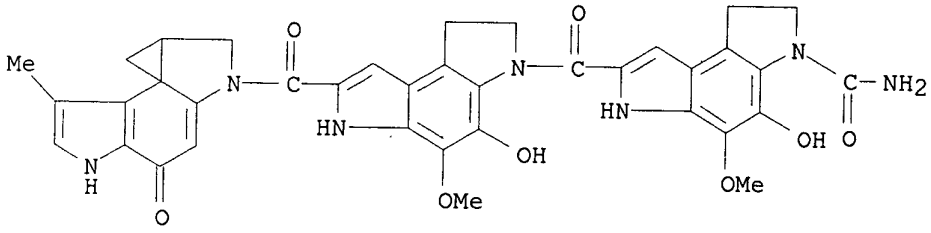
IT 521105-50-0 521105-51-1 521105-52-2 521105-53-3 521105-54-4, 5: PN: US6559125 SEQID: 5 unclaimed **DNA** 521105-55-5, 6: PN: US6559125 SEQID: 6 unclaimed **DNA** 521105-56-6 521105-57-7 521105-58-8 521105-59-9 521105-60-2 521105-61-3 521105-62-4 521105-63-5 521105-64-6 521105-65-7 521105-66-8 521105-67-9 521105-68-0 521105-69-1 521105-70-4 521105-71-5 521105-72-6 521105-73-7

RL: PRP (Properties)
(unclaimed nucleotide sequence; polyamide-alkylator conjugates for selective alkylation of double-stranded **DNA**)

IT **69866-21-3DP**, (+)-CC-1065, polyamide conjugates
RL: BUU (Biological use, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); USES (Uses)
(polyamide-alkylator conjugates for selective alkylation of double-stranded **DNA**)

RN 69866-21-3 HCAPLUS

CN Benzo[1,2-b:4,3-b']dipyrrole-3(2H)-carboxamide, 7-[[1,6-dihydro-4-hydroxy-5-methoxy-7-[(4,5,8,8a-tetrahydro-7-methyl-4-oxocyclopropa[c]pyrrolo[3,2-e]indol-2(1H)-yl)carbonyl]benzo[1,2-b:4,3-b']dipyrrol-3(2H)-yl]carbonyl]-1,6-dihydro-4-hydroxy-5-methoxy-, (7bR,8aS)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 103 THERE ARE 103 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 2 OF 8 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:242708 HCAPLUS
DOCUMENT NUMBER: 138:315370
TITLE: Inhibition of Transcription at a Coding Sequence by Alkylating Polyamide
AUTHOR(S): Oyoshi, Takanori; Kawakami, Wakana; Narita, Akihiko; Bando, Toshikazu; Sugiyama, Hiroshi
CORPORATE SOURCE: Division of Biofunctional Molecules, Tokyo Medical and Dental University, Tokyo, 101-0062, Japan
SOURCE: Journal of the American Chemical Society (2003), 125(16), 4752-4754
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Transcription from **DNA** sequence-specifically alkylated by a hairpin polyamide (ImPyPy-.gamma.-ImPyLDu86, 1) was investigated. High-resoln. polyacrylamide gel electrophoresis demonstrated that conjugate 1 alkylated a 993-bp **DNA** fragment, in accordance with the Py-Im recognition rule, predominantly at the one match site on the GFP-encoding strand and at four sites (I'-IV') on the noncoding strand. Alkylation of **DNA** inhibited the formation of full-length mRNA and caused the transcription of truncated mRNA. Polyacrylamide gel electrophoresis demonstrated that the length of the truncated mRNA was consistent with the alkylated site on the coding strand. Complete inhibition of full-length mRNA synthesis was obsd. in the presence of 50 nM 1. In clear contrast, the hydrolyzed deriv. of 1, designated 2,

produced no truncated mRNA, nor did it significantly retard transcription: >80% transcription of full-length mRNA was obsd. at 50 nM. These results clearly indicate that inhibition of transcription can be achieved with alkylating Py-Im polyamide even in the coding regions of genes.

CC 3-1 (Biochemical Genetics)
Section cross-reference(s): 35

ST hairpin polyamide **DNA** alkylation transcription inhibition GFP gene

IT Alkylation
(biochem., of **DNA**, by polyamide; inhibition of transcription at coding sequence by alkylating polyamide)

IT **Polyamides, biological studies**
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(used to modify **DNA** template; inhibition of transcription at coding sequence by alkylating polyamide)

IT **514821-08-0** 514821-09-1
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(used to alkylate **DNA**; inhibition of transcription at coding sequence by alkylating polyamide)

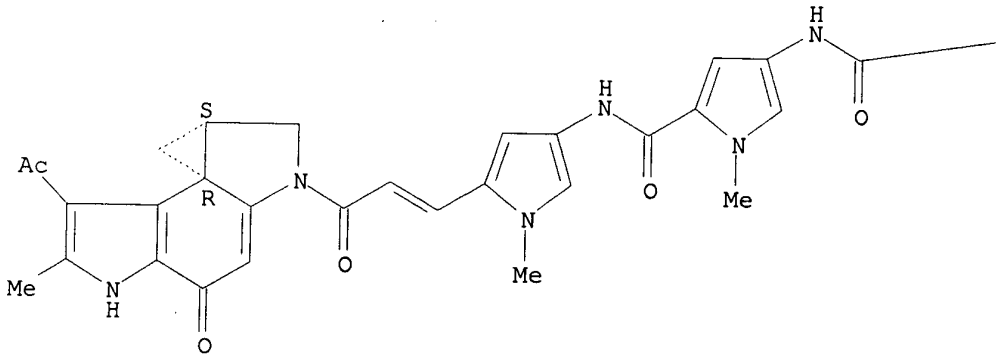
IT **514821-08-0**
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(used to alkylate **DNA**; inhibition of transcription at coding sequence by alkylating polyamide)

RN 514821-08-0 HCAPLUS

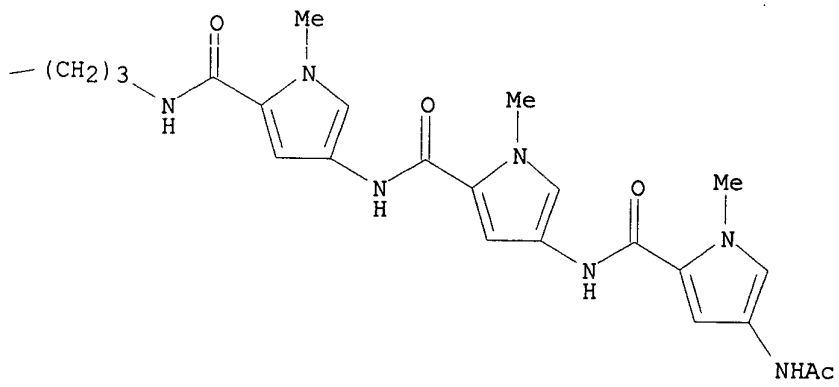
CN 1H-Pyrrole-2-carboxamide, 4-[[[4-(acetylamino)-1-methyl-1H-pyrrol-2-yl]carbonyl]amino]-N-[5-[[[4-[[5-[[[5-[3-[(7bR,8aS)-7-acetyl-4,5,8,8a-tetrahydro-6-methyl-4-oxocyclopropa[c]pyrrolo[3,2-e]indol-2(1H)-yl]-3-oxo-1-propenyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]-4-oxobutyl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]-1-methyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

PAGE 1-A



PAGE 1-B

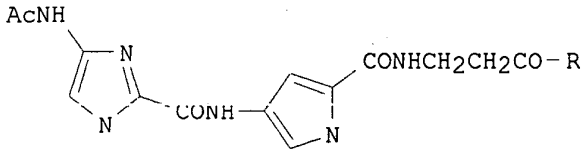


REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 3 OF 8 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:5952 HCAPLUS
DOCUMENT NUMBER: 138:73256
TITLE: Method of the solid phase synthesis of pyrrole-imidazole polyamide
INVENTOR(S): Sugiyama, Hiroshi; Iida, Hirokazu; Saito, Isao; Saito, Takashi
PATENT ASSIGNEE(S): Japan Science and Technology Corporation, Japan
SOURCE: PCT Int. Appl., 47 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003000683	A1	20030103	WO 2002-JP1775	20020227
W: CA, JP, US				
PRIORITY APPLN. INFO.:			JP 2001-190957 A	20010625

GI



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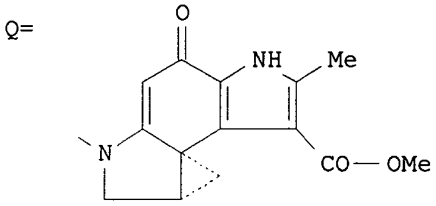


AB It is intended to provide a method of producing a pyrrole-imidazole polyamide whereby a longer pyrrole-imidazole polyamide can be conveniently synthesized and a peptide (protein) can be easily incorporated. According to this method, a pyrrole-imidazole polyamide having a carboxylate group which can be cleaved from a solid phase carrier at its end, makes it possible to directly introduce various functional groups, e.g. **DNA** alkylating agents such as duocarmycins and bleomycins to provide sequence-specific **DNA** alkylating agents, and can accurately recognize **DNA** sequences can be efficiently produced. Also disclosed are a method of synthesizing a pyrrole-imidazole polyamide characterized by performing automatic synthesis using the solid-phase Fmoc method with the use of a peptide synthesizer; a pyrrole-imidazole polyamide having a carboxyl group at its end obtained by this method; a pyrrole-imidazole polyamide having a **DNA** alkylation agent transferred into the carboxyl group at the end of the above-described pyrrole-imidazole polyamide; and a sequence-specific **DNA** alkylation method characterized by using the above compd. Pyrrole-imidazole polyamides may be screened for such biol. activities as accurate recognition of **DNA** sequences for anticancer activity for targeting **DNA** sequences specific to cancer cells. Thus, N-[[4-[[(1-methyl-4-acetamido-2-imidazolyl)carbonyl]amino]-1-methyl-2-pyrrolyl]carbonyl]-.beta.-alanine (I; R = OH) was prepd. by above process using Fmoc-.beta.-alanine bound on a Wang resin, 4-[(9-fluorenylmethoxycarbonyl)amino]-1-methyl-2-pyrrole-2-carboxylic acid, and 4-[(9-fluorenylmethoxycarbonyl)amino]-1-methyl-2-imidazole-2-carboxylic acid, converted into an imidazole ester I (R = imidazol-1-yl), and condensed with the segment A of Du-86 to give I (R = Q). I (R = Q) in vitro recognized and alkylated 5'-TAAA-3' of 5'-CTATAAAGA-3'.

IC ICM C07D403-12
ICS C07D403-14; C07D207-34; C07D487-04; C07D405-14

CC 28-9 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1

ST pyrrole imidazole polyamide solid phase synthesis; solid phase Fmoc method pyrrole imidazole polyamide prepn; sequence specific **DNA** alkylating agent pyrrole imidazole polyamide prepn; anticancer DU86 segment A conjugate pyrrole imidazole polyamide prepn

IT **Nucleic acid** hybridization
(**DNA-DNA**; method of solid-phase synthesis of pyrrole-imidazole polyamides and DU-86 segment A conjugate with

pyrrole-imidazole polyamides as sequence-specific **DNA** alkylating agents)

IT Alkylating agents, biological
Neoplasm
(**DNA**; method of solid-phase synthesis of pyrrole-imidazole polyamides and DU-86 segment A conjugate with pyrrole-imidazole polyamides as sequence-specific **DNA** alkylating agents)

IT Drug delivery systems
(anticancer; method of solid-phase synthesis of pyrrole-imidazole polyamides and DU-86 segment A conjugate with pyrrole-imidazole polyamides as sequence-specific **DNA** alkylating agents)

IT Solid phase synthesis
(automated; method of solid-phase synthesis of pyrrole-imidazole polyamides and DU-86 segment A conjugate with pyrrole-imidazole polyamides as sequence-specific **DNA** alkylating agents)

IT Antitumor agents
(method of solid-phase synthesis of pyrrole-imidazole polyamides and DU-86 segment A conjugate with pyrrole-imidazole polyamides as sequence-specific **DNA** alkylating agents)

IT **Deoxyribonucleotides**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(method of solid-phase synthesis of pyrrole-imidazole polyamides and DU-86 segment A conjugate with pyrrole-imidazole polyamides as sequence-specific **DNA** alkylating agents)

IT **Polyamides, preparation**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(method of solid-phase synthesis of pyrrole-imidazole polyamides and DU-86 segment A conjugate with pyrrole-imidazole polyamides as sequence-specific **DNA** alkylating agents)

IT 480433-85-0 481117-39-9 481117-40-2 481117-41-3 481117-42-4 481768-13-2
RL: RCT (Reactant); RACT (Reactant or reagent)
(alkylation; method of solid-phase synthesis of pyrrole-imidazole polyamides and DU-86 segment A conjugate with pyrrole-imidazole polyamides as sequence-specific **DNA** alkylating agents)

IT **480433-79-2P 480433-81-6P 480433-83-8P**
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(method of solid-phase synthesis of pyrrole-imidazole polyamides and DU-86 segment A conjugate with pyrrole-imidazole polyamides as sequence-specific **DNA** alkylating agents)

IT 480433-84-9P
RL: BUU (Biological use, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); USES (Uses)
(method of solid-phase synthesis of pyrrole-imidazole polyamides and DU-86 segment A conjugate with pyrrole-imidazole polyamides as sequence-specific **DNA** alkylating agents)

IT 56-12-2, 4-Aminobutyric acid, reactions 76-02-8, Trichloroacetyl chloride 96-54-8, 1-Methylpyrrole 35737-10-1D, N-(9-Fluorenylmethoxycarbonyl)-.beta.-alanine, Wang resin-bound 82911-69-1, 9-Fluorenylmethyl succinimidyl carbonate 116821-47-7D, 4-[(9-Fluorenylmethoxycarbonyl)amino]butanoic acid, resin-bound 186760-22-5
RL: RCT (Reactant); RACT (Reactant or reagent)

(method of solid-phase synthesis of pyrrole-imidazole polyamides and DU-86 segment A conjugate with pyrrole-imidazole polyamides as sequence-specific **DNA** alkylating agents)

IT 616-47-7P, 1-Methylimidazole 13138-76-6P, Methyl 4-nitro-1-methylpyrrole-2-carboxylate 21898-65-7P, 1-Methyl-2-trichloroacetylpyrrole 30148-23-3P, 1-Methyl-2-trichloroacetylimidazole 116821-47-7P, 4-[(9-Fluorenylmethoxycarbonyl)amino]butyric acid 120095-64-9P, 1-Methyl-4-nitro-2-trichloroacetylimidazole 120122-47-6P, 1-Methyl-4-nitro-2-trichloroacetylpyrrole 169770-25-6P, Methyl 4-nitro-1-methylimidazole-2-carboxylate 180258-45-1P, Methyl 4-amino-1-methylpyrrole-2-carboxylate hydrochloride 195387-29-2P, 4-[(9-Fluorenylmethoxycarbonyl)amino]-1-methyl-2-pyrrole-2-carboxylic acid 252206-28-3P, 4-[(9-Fluorenylmethoxycarbonyl)amino]-1-methyl-2-imidazole-2-carboxylic acid 480433-71-4P, Methyl 4-amino-1-methylimidazole-2-carboxylate hydrochloride 480433-72-5P 480433-73-6P 480433-74-7P 480433-75-8P 480433-76-9P 480433-77-0P 480433-78-1P 480433-80-5P 480433-82-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(method of solid-phase synthesis of pyrrole-imidazole polyamides and DU-86 segment A conjugate with pyrrole-imidazole polyamides as sequence-specific **DNA** alkylating agents)

IT **480433-79-2P 480433-81-6P 480433-83-8P**
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

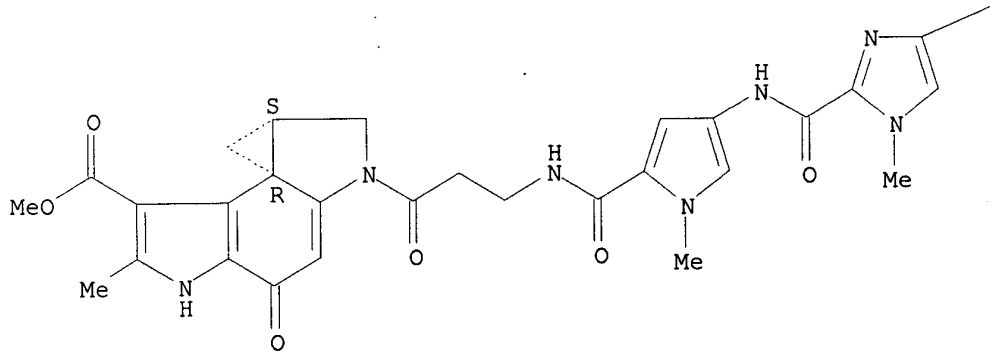
(method of solid-phase synthesis of pyrrole-imidazole polyamides and DU-86 segment A conjugate with pyrrole-imidazole polyamides as sequence-specific **DNA** alkylating agents)

RN 480433-79-2 HCAPLUS

CN Cyclopropa[c]pyrrolo[3,2-e]indole-7-carboxylic acid, 2-[3-[[[4-[[[4-(acetylamino)-1-methyl-1H-imidazol-2-yl]carbonyl]amino]-1-methyl-1H-pyrrol-2-yl]carbonyl]amino]-1-oxopropyl]-1,2,4,5,8,8a-hexahydro-6-methyl-4-oxo-, methyl ester, (7bR,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



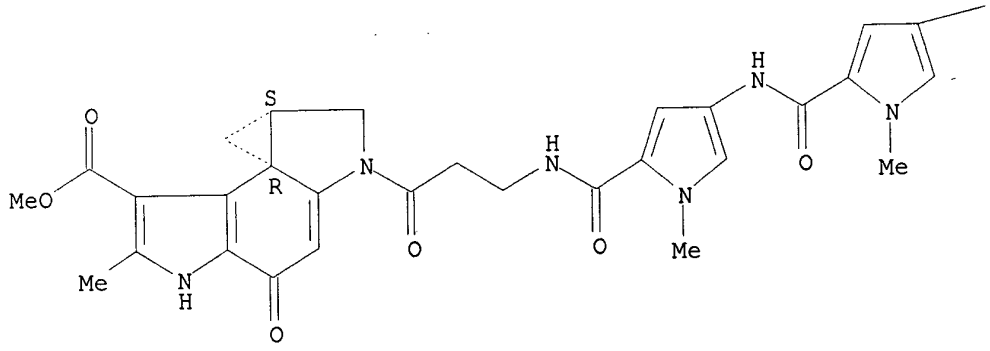
PAGE 1-B

NHAc

RN 480433-81-6 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-7-carboxylic acid, 1,2,4,5,8,8a-hexahydro-2-[3-[[[1-methyl-4-[[[1-methyl-4-[[3-[[[1-methyl-4-[[(1-methyl-1H-imidazol-2-yl)carbonyl]amino]-1H-imidazol-2-yl]carbonyl]amino]-1-oxopropyl]amino]-1H-pyrrol-2-yl]carbonyl]amino]-1H-pyrrol-2-yl]carbonyl]amino]-1-oxopropyl]-4-oxo-, methyl ester, (7bR,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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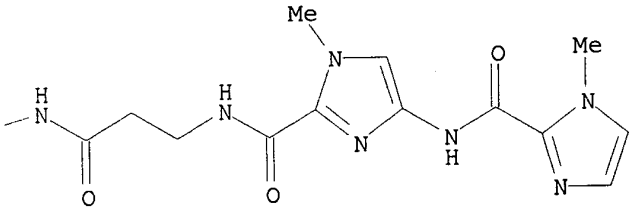
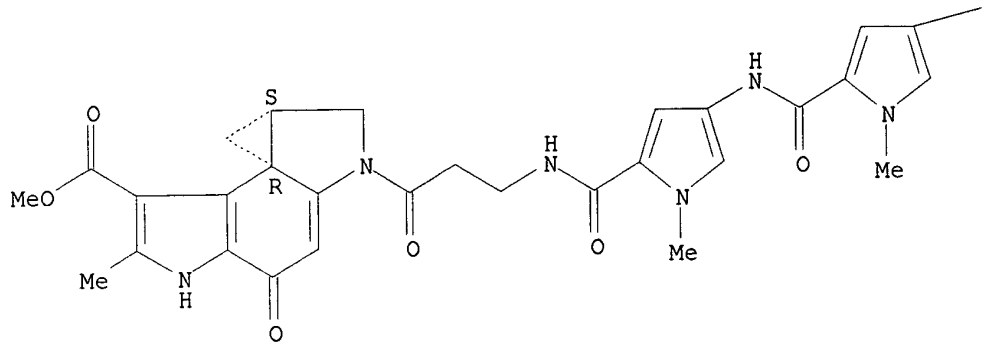


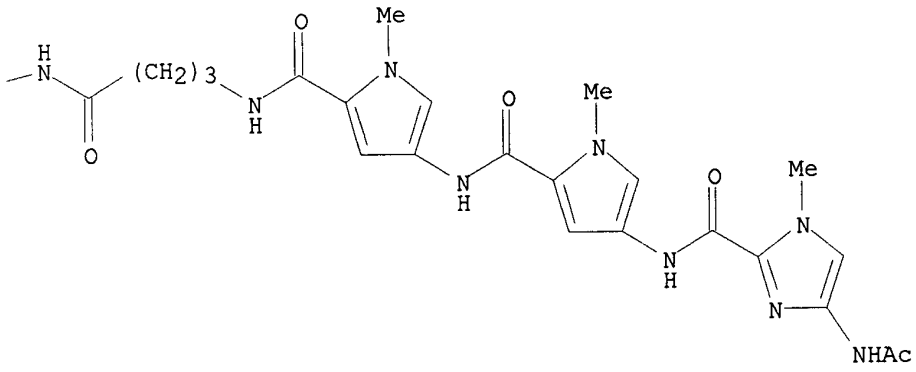
RN 480433-83-8 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-7-carboxylic acid, 2-[3-[[[4-[[[4-[[[4-[[[4-[[[4-(acetylamino)-1-methyl-1H-imidazol-2-yl]carbonyl]amino]-1-methyl-1H-pyrrol-2-yl]carbonyl]amino]-1-methyl-1H-pyrrol-2-yl]carbonyl]amino]-1-oxobutyl]amino]-1-methyl-1H-pyrrol-2-yl]carbonyl]amino]-1-methyl-1H-pyrrol-2-yl]carbonyl]amino]-1-oxopropyl]-1,2,4,5,8,8a-hexahydro-6-methyl-4-oxo-, methyl ester, (7bR,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 4 OF 8 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:964476 HCAPLUS
DOCUMENT NUMBER: 138:39101
TITLE: Preparation of antipathogenic poly-pyrrole-benzamide compounds
INVENTOR(S): Burli, Roland W.; Kaizerman, Jacob A.; Jones, Peter
PATENT ASSIGNEE(S): Genesoft Inc., USA
SOURCE: PCT Int. Appl., 106 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002101007	A2	20021219	WO 2002-US17951	20020606
WO 2002101007	A3	20030327		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-298206P P 20010613
US 2001-342309P P 20011221

OTHER SOURCE(S): MARPAT 138:39101

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. I [R1 = H, F, Cl, CN, CF3, OH, N(R2)2, OR2, etc.; R2-3 = H, alkyl, heteroalkyl; n = 1-25; Y = alkylene, (hetero)arom.; Z = O, N; m = 1 if Z = O, m = 2 if Z = N] were prepd. For instance, II (prepn. given) was coupled to 4-chloro-2-fluorobenzoic acid, the product sapond. and the resulting carboxylic acid coupled to N-(2-aminoethyl)morpholine to give III. III had MIC .ltoreq. 4 .mu.g/mL against B. cereus, E. faecalis, E. faecium, S. aureus, S. epidermidis and S. pneumoniae. A no. of compds. of the invention were screened for their ability to bind to three **DNA** sites (binding data tabulated).

IC ICM C12N

CC 25-19 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
Section cross-reference(s): 1, 28, 63

IT Anti-infective agents
Antibacterial agents
Antibiotics
Drug resistance
Human
(prepn. of poly-pyrrole-benzamide and related analogs as antibiotics and **DNA** binders)

IT **Polyamides, preparation**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of poly-pyrrole-benzamide and related analogs as antibiotics and **DNA** binders)

IT 478802-25-4P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. of poly-pyrrole-benzamide and related analogs as antibiotics and **DNA** binders)

IT 478801-53-5P 478801-54-6P 478801-55-7P 478801-56-8P 478801-57-9P
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478801-81-9P 478801-83-1P 478801-85-3P 478801-87-5P 478801-90-0P
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478803-77-9P 478803-78-0P 478803-79-1P 478803-80-4P 478811-74-4P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of poly-pyrrole-benzamide and related analogs as antibiotics and **DNA** binders)

IT 122-01-0, 4-Chlorobenzoyl chloride 394-39-8 446-30-0 2038-03-1, 4-Morpholineethanamine 2810-04-0 3167-49-5, 6-Amino-3-pyridinecarboxylic acid 3647-69-6, 4-(2-Chloroethyl)morpholine hydrochloride 4023-00-1, 1H-Pyrazole-1-carboximidamide 5050-41-9, 1-(2-Chloroethyl)pyrrolidine 5930-92-7 6940-76-7, 1-Chloro-3-iodopropane 24340-76-9 27578-60-5, 1-Piperidineethanamine 32955-21-8 36778-15-1 53391-50-7 53515-36-9, 4-Thiomorpholineethanamine 66493-39-8 72083-62-6 72482-64-5, 2,4-Difluorobenzoyl chloride 85406-53-7 111331-82-9 180258-45-1 203586-94-1 292068-69-0 474417-98-6 474418-04-7 478400-09-8 478493-16-2 478804-05-6 478804-06-7 478804-07-8 478804-08-9 478804-09-0 478804-10-3 478804-11-4
RL: RCT (Reactant); RACT (Reactant or reagent)

(prepn. of poly-pyrrole-benzamide and related analogs as antibiotics and **DNA** binders)

IT 5751-84-8P 52205-57-9P 66117-32-6P 374694-40-3P 474417-85-1P
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478493-09-3P 478803-81-5P 478803-82-6P 478803-83-7P 478803-84-8P
478803-85-9P 478803-86-0P 478803-87-1P 478803-88-2P 478803-89-3P
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478804-00-1P 478804-01-2P 478804-02-3P 478804-03-4P 478804-04-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)

(prepn. of poly-pyrrole-benzamide and related analogs as antibiotics and **DNA** binders)

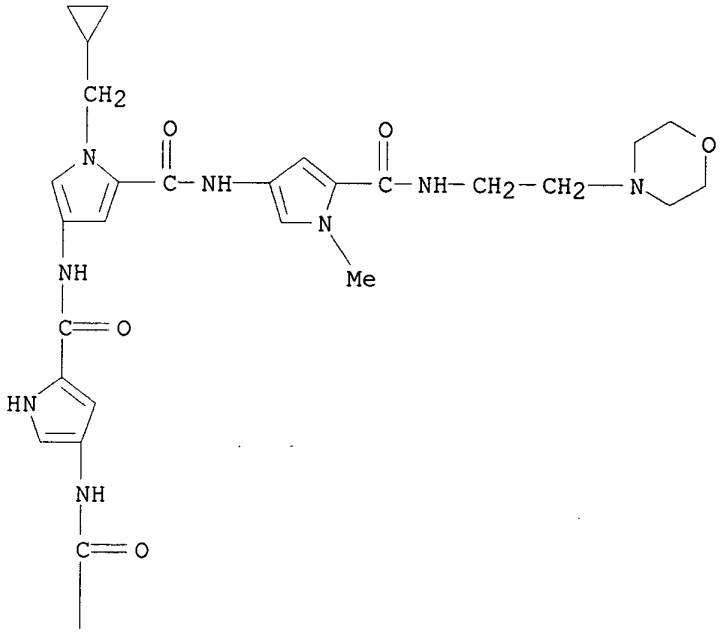
IT **478803-02-0P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

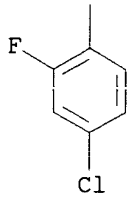
(prepn. of poly-pyrrole-benzamide and related analogs as antibiotics and **DNA** binders)

RN 478803-02-0 HCAPLUS

CN 1H-Pyrrole-2-carboxamide, 4-[[[4-[(4-chloro-2-fluorobenzoyl)amino]-1H-pyrrol-2-yl]carbonyl]amino]-1-(cyclopropylmethyl)-N-[1-methyl-5-[[[2-(4-morpholinyl)ethyl]amino]carbonyl]-1H-pyrrol-3-yl]- (9CI) (CA INDEX NAME)

PAGE 1-A





L30 ANSWER 5 OF 8 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:964348 HCAPLUS
DOCUMENT NUMBER: 138:39181
TITLE: Preparation of poly-pyrrole substituted benzothiophene compounds having antiinfective activity
INVENTOR(S): Burli, Roland W.; Baird, Eldon E.; Taylor, Matthew J.; Kaizerman, Jacob A.; Hu, Wenhao
PATENT ASSIGNEE(S): Genesoft, Inc., USA
SOURCE: PCT Int. Appl., 74 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002100852	A1	20021219	WO 2002-US17952	20020606

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-298206P P 20010613
US 2001-325134P P 20010924
OTHER SOURCE(S): MARPAT 138:39181
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. I [R5 = H, F, Cl, Br, I, CN, OH, NH2, etc.; n = 1-25; Y = alkylene, (hetero)arom.; Z = O, N; m = 1 if Z = O, m = 2 if Z = N; R2 = H, alkyl, heteroalkyl] are prepd. For instance, II (prior art) was coupled to 3-chlorobenzothiophene-2-carboxylic acid (DMF, HBTU, i-Pr2NEt, 30 min, 37.degree.) to give III. I are **DNA** binding compds. exhibiting antibacterial activity. III has MIC .ltoreq. 4 .mu.g/mL against B. cereus, S. aureus, S. epidermidis, E. faecium, and S. pneumoniae.
IC ICM C07D333-56

ICS C07D405-00; C07D413-00; A61K031-385; A61K031-40; A61K031-535
CC 27-9 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1, 28, 34, 63
ST benzothiophene antiinfective antibacterial **DNA** binding polypyrrole prepn
IT Anti-infective agents
Antibacterial agents
Drug resistance
Fungicides
Human
(prepn. of poly-pyrrole substituted benzothiophene compds. having antiinfective and **DNA** binding activity)
IT **DNA**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(prepn. of poly-pyrrole substituted benzothiophene compds. having antiinfective and **DNA** binding activity)
IT **Polyamides, preparation**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of poly-pyrrole substituted benzothiophene compds. having antiinfective and **DNA** binding activity)
IT 478398-58-2P 478398-59-3P 478398-60-6P 478398-61-7P 478398-62-8P
478398-63-9P 478398-64-0P 478398-66-2P 478398-68-4P 478398-70-8P
478398-72-0P 478398-74-2P 478398-76-4P 478398-78-6P 478398-80-0P
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478398-87-7P 478398-88-8P 478398-89-9P 478398-90-2P 478398-91-3P
478398-92-4P 478398-93-5P 478398-94-6P 478398-95-7P 478398-96-8P
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478399-14-3P 478399-17-6P 478399-18-7P 478399-19-8P 478399-20-1P
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478399-89-2P 478399-90-5P 478399-91-6P 478399-92-7P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of poly-pyrrole substituted benzothiophene compds. having antiinfective and **DNA** binding activity)
IT 2038-03-1, 4-Morpholineethanamine 3647-69-6 5930-92-7 21211-22-3
21815-91-8 52995-76-3 53391-50-7 58095-77-5 120122-47-6
478400-06-5 478400-07-6 478400-08-7 478400-09-8 478400-10-1
478400-11-2
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of poly-pyrrole substituted benzothiophene compds. having antiinfective and **DNA** binding activity)

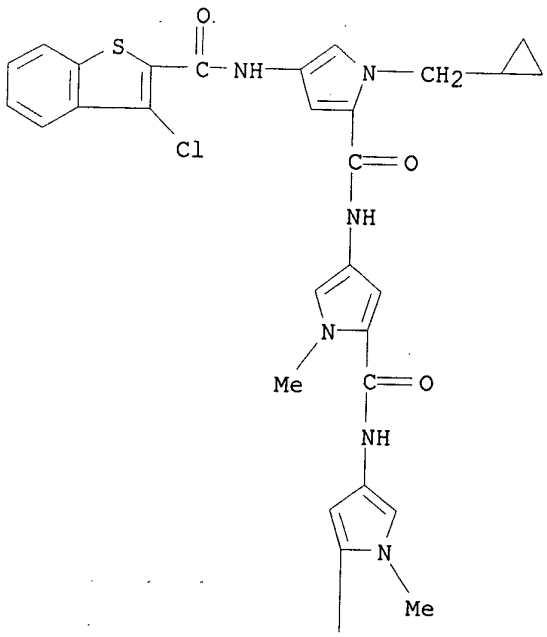
IT 4791-82-6P 137278-46-7P 474418-02-5P 474418-04-7P 478399-93-8P
478399-94-9P 478399-97-2P 478399-98-3P 478399-99-4P 478400-00-9P
478400-01-0P 478400-02-1P 478400-03-2P 478400-04-3P 478400-05-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of poly-pyrrole substituted benzothiophene compds. having antiinfective and **DNA** binding activity)

IT **478399-41-6P 478399-43-8P 478399-45-0P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of poly-pyrrole substituted benzothiophene compds. having antiinfective and **DNA** binding activity)

RN 478399-41-6 HCAPLUS

CN 1H-Pyrrole-2-carboxamide, 4-[[[4-[[(3-chlorobenzo[b]thien-2-yl)carbonyl]amino]-1-(cyclopropylmethyl)-1H-pyrrol-2-yl]carbonyl]amino]-1-methyl-N-[1-methyl-5-[[[2-(4-morpholinyl)ethyl]amino]carbonyl]-1H-pyrrol-3-yl]- (9CI) (CA INDEX NAME)

PAGE 1-A



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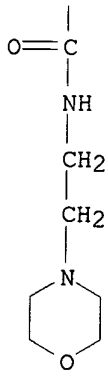
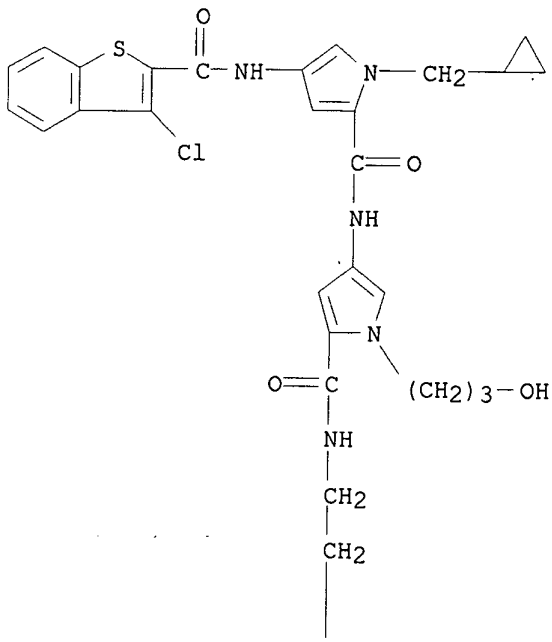


RN 478399-43-8 HCAPLUS
CN 1H-Pyrrole-2-carboxamide, 4-[[(3-chlorobenzo[b]thien-2-yl)carbonyl]amino]-1-(cyclopropylmethyl)-N-[1-(3-hydroxypropyl)-5-[[[2-(1-piperidinyl)ethyl]amino]carbonyl]-1H-pyrrol-3-yl]- (9CI) (CA INDEX NAME)

PAGE 1-A



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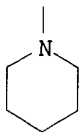

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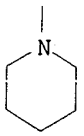
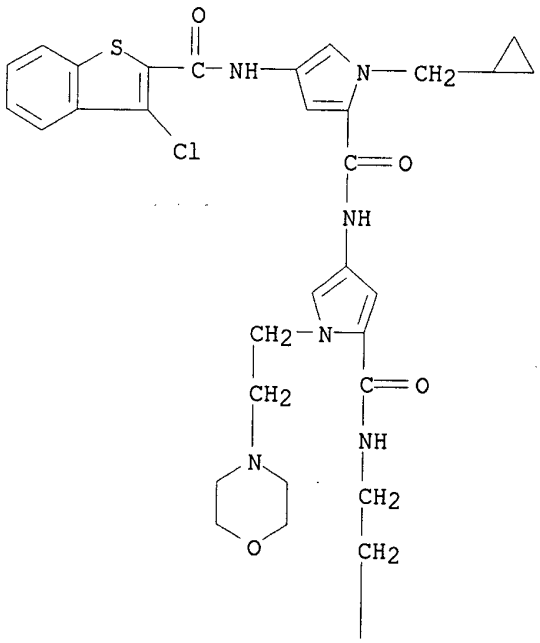


RN 478399-45-0 HCAPLUS
CN 1H-Pyrrole-2-carboxamide, 4-[[(3-chlorobenzo[b]thien-2-yl)carbonyl]amino]-1-(cyclopropylmethyl)-N-[1-[2-(4-morpholinyl)ethyl]-5-[[[2-(1-piperidinyl)ethyl]amino]carbonyl]-1H-pyrrol-3-yl]- (9CI) (CA INDEX NAME)

PAGE 1-A



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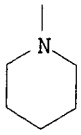


REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L30 ANSWER 6 OF 8 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:615567 HCAPLUS
DOCUMENT NUMBER: 137:169795

TITLE: Preparation of polyamide analogs as antibacterial, antifungal, and antiparasitic agents

INVENTOR(S): Velligan, Mark D.; Khorlin, Alexander; Dyatkina, Natalia B.; Shi, Dong-Fang; Botyanszki, Janos; Liehr, Sebastian

PATENT ASSIGNEE(S): Genelab Technologies, Inc., USA

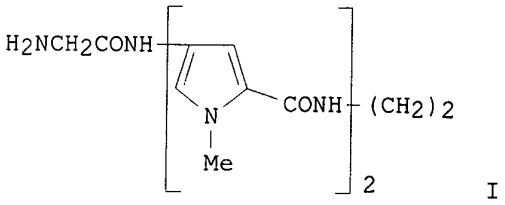
SOURCE: PCT Int. Appl., 119 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002062755	A2	20020815	WO 2001-US45873	20011227
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2002198254	A1	20021226	US 2001-26963	20011227

PRIORITY APPLN. INFO.: US 2000-258842P P 20001227
OTHER SOURCE(S): MARPAT 137:169795

GI



I

AB Compds. R1NH-Ar1-CO(NH-Ar2-CO)nNH-L-NH(CO-Ar3-NH)mCO-Ar4-NHR2 [R1, R2 = H, alkyl, (un)substituted alkanoyl or carbamoyl, at least one of which can form a salt; m, n = 0-4; Ar1-Ar4 = optionally substituted (hetero)arylene; L = alkylene which may be substituted by CONHR4, CONHNHR6, NHR9 (R4, R6, R9 = H, alkyl, aryl, etc.), or a guanidino group or L = (alkylene)x-Z-(alkylene)y-(Za)z, where x, y, and z = 0-2 and Z and Za = phenylene, cycloalkylene optionally fused to one or two phenylene ring(s), heterocyclene, O, S, NR10 (R10 = H, alkyl, cycloalkylamino, etc.), CONH or NHCO, provided that when Z and/or Za is NR10, it is sepd. from another nitrogen atom by at least two carbon atoms] or their pharmaceutically-acceptable salts were prepd. as novel antibacterial/antifungal/antiparasitic agents. Thus, compd I was prepd. by a multistep sequence involving coupling reactions of Me 4-amino-1-methyl-1H-pyrrole-2-carboxylate, N-(tert-butoxycarbonyl)glycine pentafluorophenyl ester, and ethylenediamine. Compd I showed min. inhibitory concn. values >45.5 against various bacterial strains.

IC ICM C07D207-00
CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1, 27, 63
IT **DNA**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(binding; prepn. of polyamide analogs as antibacterial, antifungal, and antiparasitic agents)
IT **Polyamides, preparation**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of polyamide analogs as antibacterial, antifungal, and antiparasitic agents)
IT **386252-76-2P** 446881-90-9P 446881-91-0P 446881-92-1P
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446883-42-7P 446883-43-8P 446883-44-9P 446883-45-0P 446883-72-3P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of polyamide analogs as antibacterial, antifungal, and antiparasitic agents)
IT 79-08-3, Bromoacetic acid 99-56-9, 4-Nitro 1 2 benzenediamine 105-83-9
107-15-3, Ethylenediamine, reactions 109-76-2, 1,3-Propanediamine
110-60-1, 1,4-Butanediamine 124-09-4, 1,6-Hexanediamine, reactions
305-03-3, Chlorambucil 373-44-4, 1,8-Octanediamine 525-64-4,
2,7-Diaminofluorene 539-48-0, 1,4-Benzenedimethanamine 951-87-1,
meso-1,2-Diphenylethylenediamine 1477-55-0, 1,3-Benzenedimethanamine
1761-71-3 2549-93-1, 1,4-Cyclohexanedimethanamine 2579-20-6,
1,3-Cyclohexanedimethanamine 2615-25-0, trans 1 4 Cyclohexanediamine
2783-17-7, 1,12-Dodecanediamine 3303-84-2 4023-00-1, Pyrazole 1
carboxamidine 4023-02-3, 1h Pyrazole 1 carboxamidine hydrochloride
4420-88-6 4530-20-5 4963-47-7, Tris(3-aminopropyl)amine 6852-78-4, r

1,2-Propanediamine 7209-38-3, 1,4-Piperazinedipropanamine 7693-46-1, 4-Nitrophenyl chloroformate 13138-76-6 13734-41-3 13880-36-9, 1,2-Hexadecanediamine 14533-84-7, Pentafluorophenyl trifluoroacetate 15761-39-4 15967-72-3, s 1,2-Propanediamine 19826-45-0 20485-43-2 32388-19-5, L-Lysinamide 32926-43-5 42601-04-7, 3,4-Difluorophenyl isocyanate 50903-47-4 57294-38-9 68262-71-5 77716-11-1 77716-16-6 83468-83-1 84624-27-1 113737-76-1 195387-29-2 446882-30-0 446882-39-9D, resin-bound 446883-54-1 446883-55-2 446883-56-3 446883-57-4 446883-58-5 446883-59-6 446883-60-9 446883-61-0 446883-62-1 446883-63-2 446883-64-3 446883-65-4 446883-66-5 446883-67-6 **446883-71-2**
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of polyamide analogs as antibacterial, antifungal, and antiparasitic agents)

IT 4963-47-7DP, resin-bound 24370-22-7P, 2 Amino 4 nitrobenzimidazole 72083-62-6P 88473-88-5DP, 4-Nitrophenyl hydrogen carbonate, resin-bound 446881-72-7P 446881-73-8P 446881-75-0P 446881-77-2P 446881-79-4P 446881-82-9P 446881-84-1P 446881-86-3P 446881-88-5P 446882-30-0DP, resin-bound 446882-31-1DP, resin-bound 446882-40-2DP, resin-bound 446882-41-3P 446882-42-4DP, resin-bound 446882-44-6DP, resin-bound 446882-53-7P **446883-21-2P 446883-22-3P 446883-23-4P 446883-24-5P 446883-25-6P 446883-32-5P 446883-33-6P** 446883-46-1P 446883-47-2P 446883-48-3P 446883-49-4P 446883-50-7P 446883-51-8P 446883-52-9P 446883-53-0P 446883-69-8P 446883-70-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of polyamide analogs as antibacterial, antifungal, and antiparasitic agents)

IT **386252-76-2P 446883-26-7P 446883-27-8P 446883-28-9P 446883-29-0P 446883-30-3P 446883-31-4P 446883-34-7P**
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of polyamide analogs as antibacterial, antifungal, and antiparasitic agents)

RN 386252-76-2 HCAPLUS
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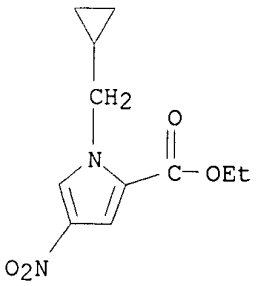

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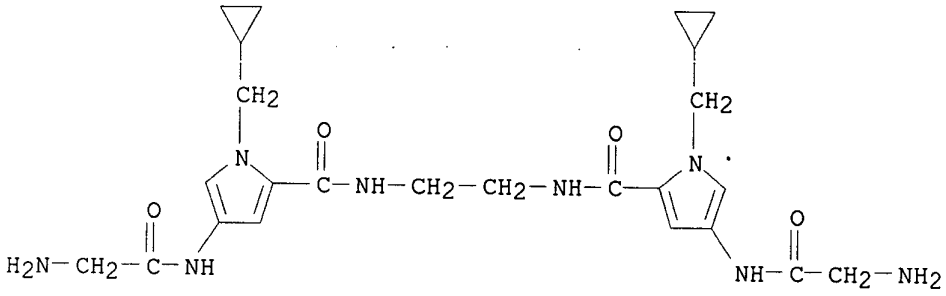

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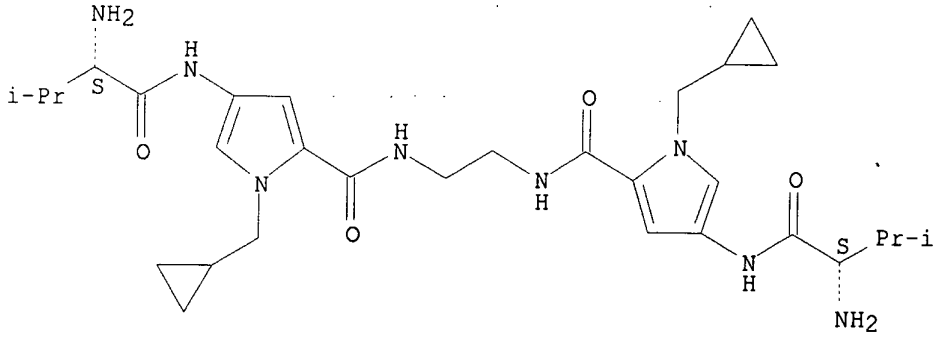
Absolute stereochemistry.



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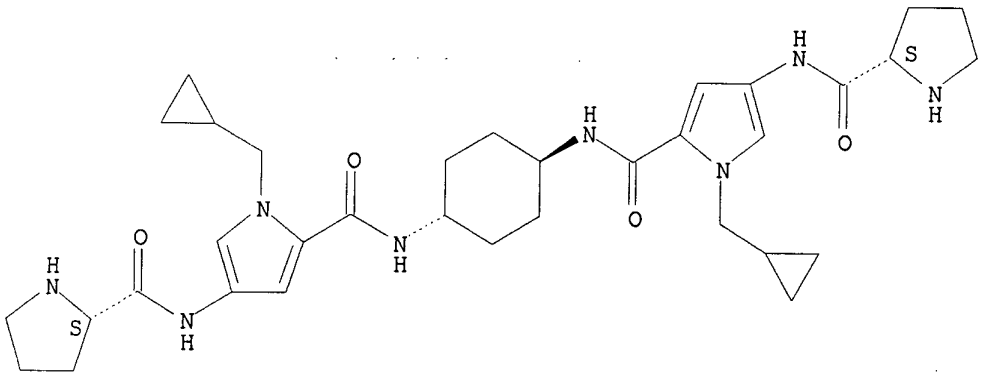
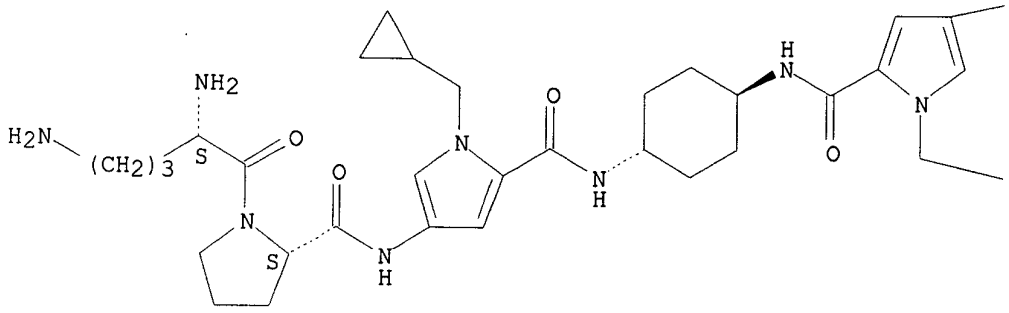
Absolute stereochemistry.



RN 446883-29-0 HCAPLUS
CN L-Prolinamide, 2,2'-[trans-1,4-cyclohexanediylbis[iminocarbonyl[1-(cyclopropylmethyl)-1H-pyrrole-2,4-diyl]]]bis[L-ornithyl- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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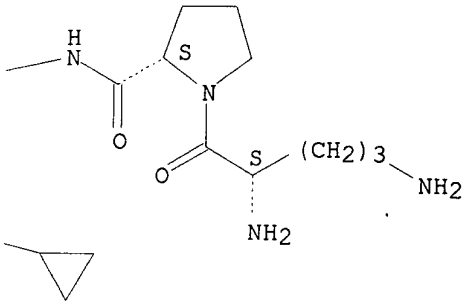
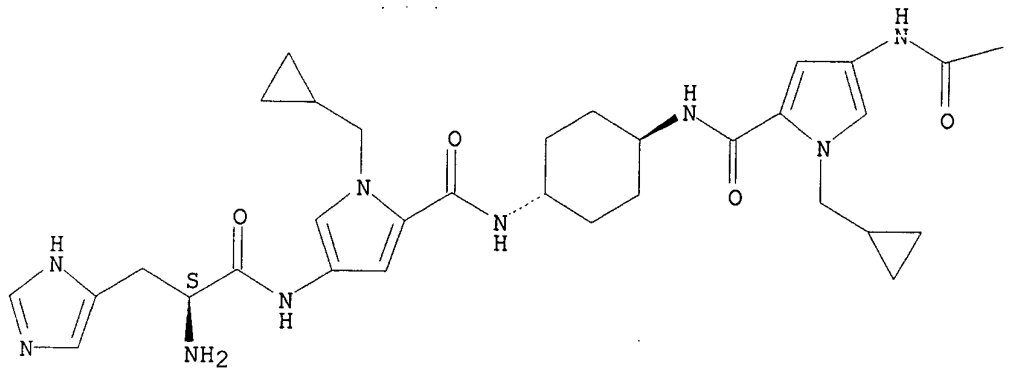


RN 446883-30-3 HCAPLUS
CN 1H-Imidazole-4-propanamide, N,N'-[trans-1,4-cyclohexanediylbis[iminocarbonyl[1-(cyclopropylmethyl)-1H-pyrrole-2,4-diyl]]]bis[.alpha.-amino-, (.alpha.S,.alpha.'S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



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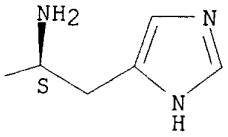
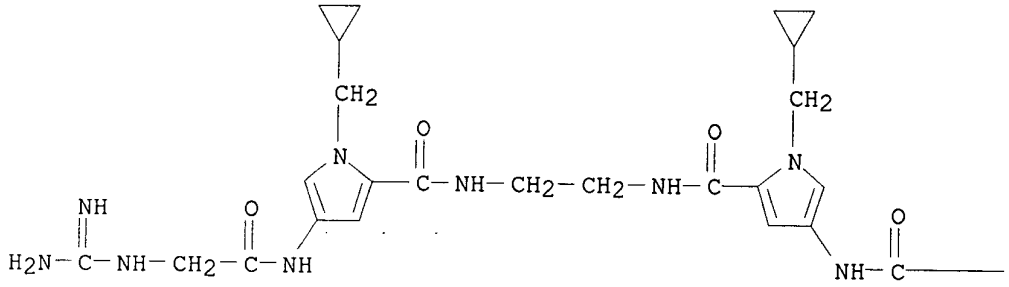


RN 446883-31-4 HCAPLUS
CN 1H-Pyrrole-2-carboxamide, N,N'-1,2-ethanediylbis[4-[[[(aminoiminomethyl)amino]acetyl]amino]-1-(cyclopropylmethyl)- (9CI) (CA INDEX NAME)

PAGE 1-A



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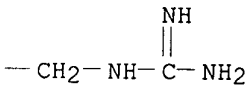
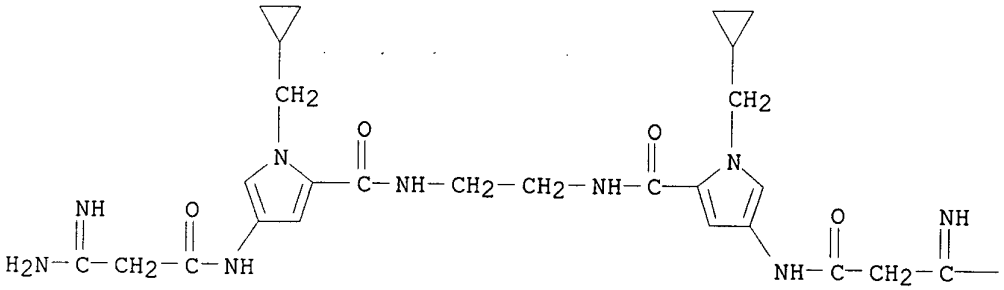


RN 446883-34-7 HCAPLUS
CN 1H-Pyrrole-2-carboxamide, N,N'-1,2-ethanediylbis[4-[(3-amino-3-imino-1-oxopropyl)amino]-1-(cyclopropylmethyl)- (9CI) (CA INDEX NAME)

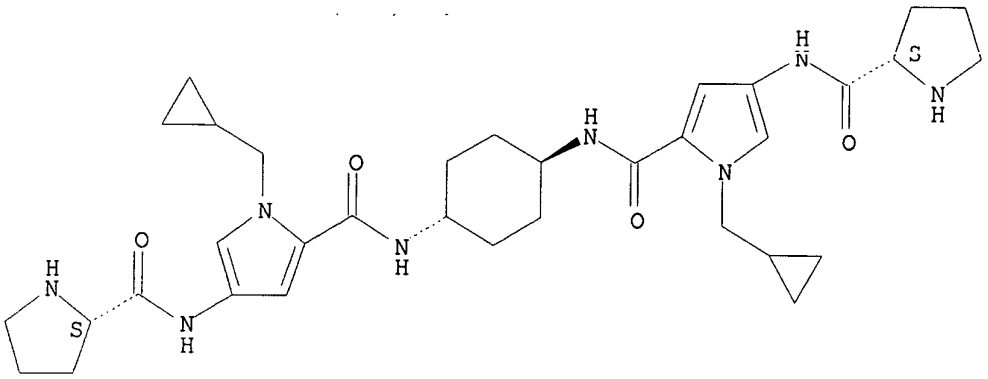
PAGE 1-A



PAGE 1-B

IT **446883-71-2**
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of polyamide analogs as antibacterial, antifungal, and antiparasitic agents)
RN 446883-71-2 HCAPLUS
CN 1H-Pyrrole-2-carboxamide, N,N'-trans-1,4-cyclohexanediylbis[1-(cyclopropylmethyl)-4-[[(2S)-2-pyrrolidinylcarbonyl]amino]-, dihydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry.

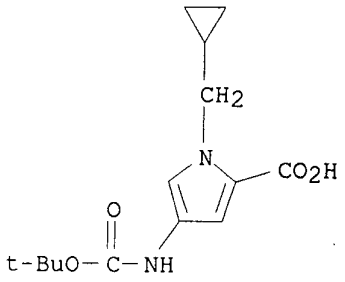


●2 HCl

IT **446883-21-2P 446883-22-3P 446883-23-4P**
446883-24-5P 446883-25-6P 446883-32-5P
446883-33-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of polyamide analogs as antibacterial, antifungal, and antiparasitic agents)

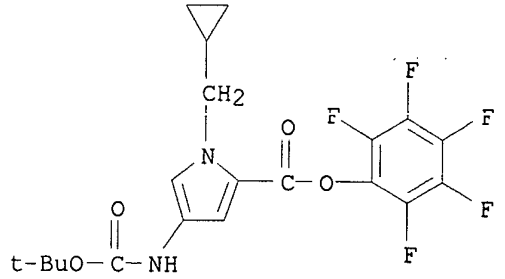
RN 446883-21-2 HCAPLUS

CN 1H-Pyrrole-2-carboxylic acid, 1-(cyclopropylmethyl)-4-[[(1,1-dimethylethoxy)carbonyl]amino]- (9CI) (CA INDEX NAME)

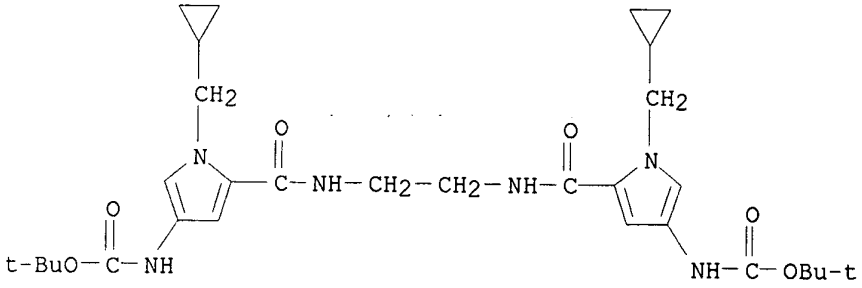


RN 446883-22-3 HCAPLUS

CN 1H-Pyrrole-2-carboxylic acid, 1-(cyclopropylmethyl)-4-[[(1,1-dimethylethoxy)carbonyl]amino]-, pentafluorophenyl ester (9CI) (CA INDEX NAME)

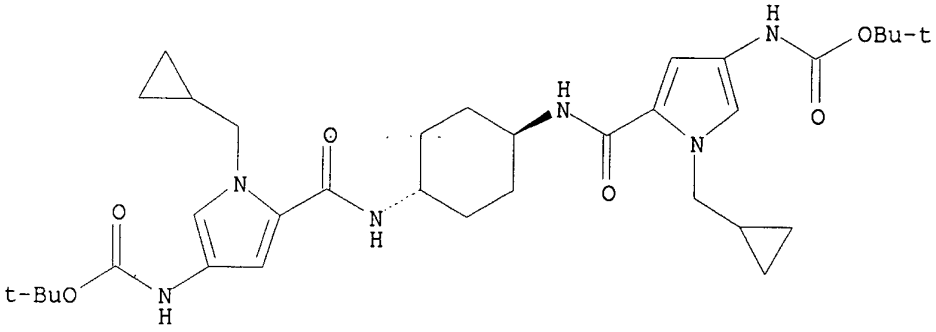


RN 446883-23-4 HCAPLUS
CN Carbamic acid, [1,2-ethanediylbis[iminocarbonyl[1-(cyclopropylmethyl)-1H-pyrrole-2,4-diyl]]]bis-, bis(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)

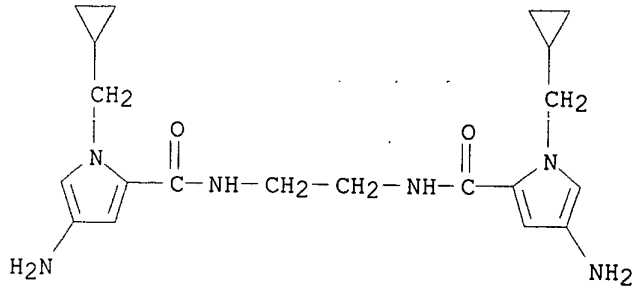


RN 446883-24-5 HCAPLUS
CN Carbamic acid, [trans-1,4-cyclohexanediylbis[iminocarbonyl[1-(cyclopropylmethyl)-1H-pyrrole-2,4-diyl]]]bis-, bis(1,1-dimethylethyl) ester (9CI) (CA INDEX NAME)

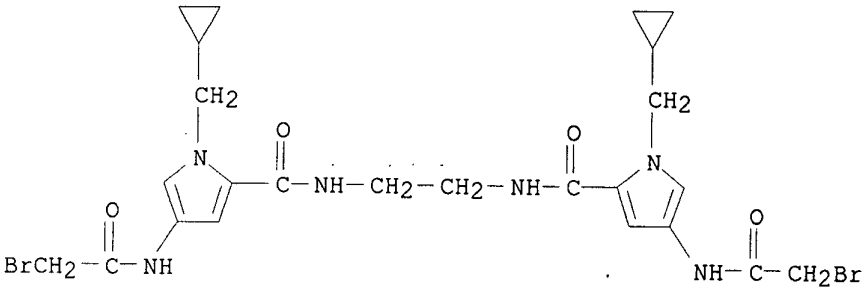
Relative stereochemistry.



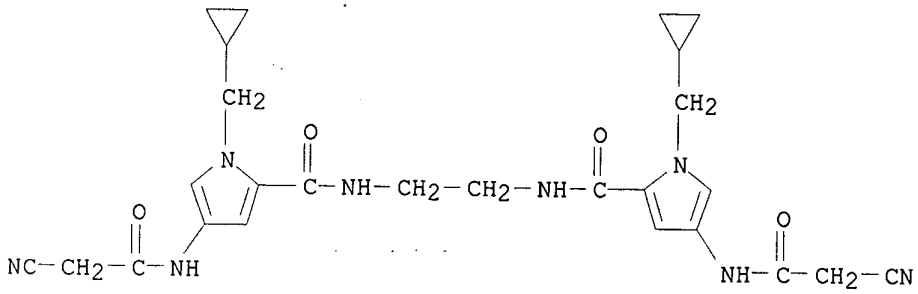
RN 446883-25-6 HCAPLUS
CN 1H-Pyrrole-2-carboxamide, N,N'-1,2-ethanediylbis[4-amino-1-(cyclopropylmethyl)- (9CI) (CA INDEX NAME)



RN 446883-32-5 HCAPLUS
CN 1H-Pyrrole-2-carboxamide, N,N'-1,2-ethanediylbis[4-[(bromoacetyl)amino]-1-(cyclopropylmethyl)- (9CI) (CA INDEX NAME)



RN 446883-33-6 HCAPLUS
CN 1H-Pyrrole-2-carboxamide, N,N'-1,2-ethanediylbis[4-[(cyanoacetyl)amino]-1-(cyclopropylmethyl)- (9CI) (CA INDEX NAME)



L30 ANSWER 7 OF 8 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:833321 HCAPLUS
DOCUMENT NUMBER: 135:371743
TITLE: Preparation of pyrrole-imidazole polyamide-duocarmycin segment conjugates as interstrand crosslinking agents for **DNA** in cancer treatment
INVENTOR(S): Sugiyama, Hiroshi; Bando, Toshikazu; Iida, Hirokazu; Saito, Isao
PATENT ASSIGNEE(S): Japan Science and Technology Corporation, Japan
SOURCE: PCT Int. Appl., 54 pp.

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001085733	A1	20011115	WO 2001-JP3756	20010501
W: US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				
JP 2001322992	A2	20011120	JP 2000-140361	20000512
EP 1281711	A1	20030205	EP 2001-926081	20010501
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY, TR				

PRIORITY APPLN. INFO.: JP 2000-140361 A 20000512
WO 2001-JP3756 W 20010501

OTHER SOURCE(S): MARPAT 135:371743
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Compds. represented by the following general formula A-L-B-X-B-L-A (I; wherein B represents a chem. structure capable of recognizing a base sequence of a **DNA**; A represents a chem. structure capable of binding to one of the bases of the **DNA**; L represents a linker by which the chem. structures A and B can be linked to each other; and X represents a spacer by which the A-L-B components can be linked to each other), by which two **DNA** strands can be interstrand-crosslinked, are prepd. Also claimed are a method of interstrand-crosslinking **DNA** by using these compds. and medicinal compns. contg. interstrand crosslinking agents of **DNA**. In the compds. I, the above chem. structure capable of recognizing a base sequence of a **DNA** is derived from pyrrole and/or imidazole and the chem. structure capable of binding to one of the bases of the **DNA** possesses a cyclopropane ring. More specifically, the compds. represented by N-[3-[4-(N-methylimidazol-2-ylcarbonylamino)-N-methylpyrrol-2-yl]acryloyl]cyclopropa[c]pyrrolo[3,2-e]indole derivs. (pyrrole-imidazole polyamide-duocarmycin segment conjugates) [II; X = CO, COCH:CHCO, CO(CH2)4CO, CO-p-C6H4-CO] are prepd. The B component in the compds. I, i.e. the 4-(N-methylimidazol-2-ylcarbonylamino)-N-methylpyrrole moiety of II, recognizes a **DNA** base sequence and is capable of specifically interstrand-crosslinking to the specific base sequence of **DNA**. These compds. inhibit the replication of **DNA** by interstrand-crosslinking to **DNA** and thereby are useful for the treatment of cancer. Interstrand-crosslinking reaction of the compds. II to **DNA** oligomers was examd. using polyacrylamide gel electrophoresis. For example, it was confirmed that II [X = CO(CH2)4CO] interstrand-crosslinked to the TGGC or GCCA or its complimentary sequence of **DNA**, in particular in the copresence of a triamide (III; X = Y = N and Z = CH; X = Y = Z = N; X = N and Y = Z = CH; X = Z = CH and Y = N).

IC ICM C07D487-04

ICS A61K031-4178; A61P035-00; C12N015-09; C07H021-04
CC 28-9 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1
ST pyrrole imidazole polyamide duocarmycin conjugate prepn anticancer; interstrand crosslinking agent **DNA**
IT Gene therapy
(cancer; prepn. of pyrrole-imidazole polyamide-duocarmycin conjugates as **DNA** interstrand crosslinking agents for treatment of cancer)
IT Antitumor agents
Crosslinking agents
(prepn. of pyrrole-imidazole polyamide-duocarmycin conjugates as **DNA** interstrand crosslinking agents for treatment of cancer)
IT **Polyamides, preparation**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of pyrrole-imidazole polyamide-duocarmycin conjugates as **DNA** interstrand crosslinking agents for treatment of cancer)
IT **DNA**
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)
(prepn. of pyrrole-imidazole polyamide-duocarmycin conjugates as **DNA** interstrand crosslinking agents for treatment of cancer)
IT 373362-36-8P, N-(3-Dimethylaminopropyl)-4-[4-[[4-[[[4-(acetylamino)-1-methyl-2-imidazolyl]carbonyl]amino]-1-methyl-2-imidazolyl]carbonyl]amino]-1-methyl-2-pyrrolecarboxamide
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(prepn. of pyrrole-imidazole polyamide-duocarmycin conjugates as **DNA** interstrand crosslinking agents for treatment of cancer)
IT **373362-22-2P 373362-24-4P 373362-26-6P 373362-27-7P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of pyrrole-imidazole polyamide-duocarmycin conjugates as **DNA** interstrand crosslinking agents for treatment of cancer)
IT 374129-69-8 374129-70-1 374129-71-2 374129-72-3 374576-26-8
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study); PROC (Process)
(prepn. of pyrrole-imidazole polyamide-duocarmycin conjugates as **DNA** interstrand crosslinking agents for treatment of cancer)
IT 339053-29-1 373362-38-0, N-(3-Dimethylaminopropyl)-4-[4-[[4-[[[4-(acetylamino)-1-methyl-2-imidazolyl]carbonyl]amino]-1-methyl-2-imidazolyl]carbonyl]amino]-1-methyl-2-imidazolecarboxamide 373362-39-1
RL: BPR (Biological process); BSU (Biological study, unclassified); MSC (Miscellaneous); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(prepn. of pyrrole-imidazole polyamide-duocarmycin conjugates as **DNA** interstrand crosslinking agents for treatment of cancer)
IT 100-20-9, Terephthaloyl chloride 109-55-7, 3-Dimethylaminopropylamine 111-50-2, Adipoyl chloride 530-62-1, 1,1'-Carbonyldiimidazole 627-63-4, Fumaroyl chloride 1192-58-1, 1-Methyl-2-pyrrolecarboxaldehyde 18711-27-8, 1-Methyl-4-nitro-2-pyrrolecarboxaldehyde 120095-64-9,

1-Methyl-4-nitro-2-(trichloroacetyl)imidazole 120122-47-6,
1-Methyl-4-nitro-2-(trichloroacetyl)pyrrole 186760-22-5
RL: RCT (Reactant); RACT (Reactant or reagent)
(prepn. of pyrrole-imidazole polyamide-duocarmycin conjugates as **DNA** interstrand crosslinking agents for treatment of cancer)

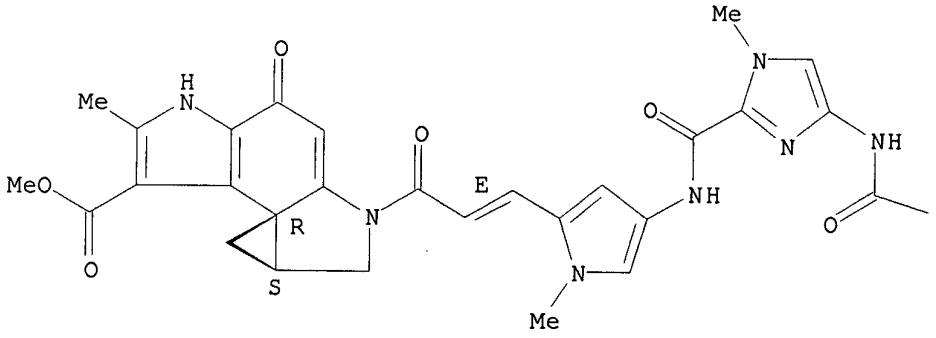
IT 65361-30-0P, N-(3-Dimethylaminopropyl)-4-nitro-1-methyl-2-pyrrolecarboxamide 78486-14-3P, N-(3-Dimethylaminopropyl)-4-amino-1-methyl-2-pyrrolecarboxamide 128484-11-7P, N-(3-Dimethylaminopropyl)-4-[[(4-nitro-1-methyl-2-imidazolyl)carbonyl]amino]-1-methyl-2-pyrrolecarboxamide 373362-02-8P, trans-3-(4-Nitro-1-methyl-2-pyrrolyl)-2-propenoic acid ethyl ester 373362-03-9P, trans-3-(4-(((4-Nitro-1-methylimidazol-2-yl)carbonyl)amino)-1-methyl-2-pyrrolyl)-2-propenoic acid ethyl ester 373362-05-1P 373362-06-2P 373362-07-3P 373362-08-4P 373362-09-5P 373362-10-8P 373362-12-0P 373362-14-2P 373362-15-3P 373362-17-5P 373362-18-6P 373362-20-0P 373362-29-9P, trans-3-(4-Amino-1-methyl-2-pyrrolyl)-2-propenoic acid ethyl ester 373362-33-5P, N-(3-Dimethylaminopropyl)-4-[4-[[4-[[[4-nitro-1-methyl-2-imidazolyl]carbonyl]amino]-1-methyl-2-imidazolyl]carbonyl]amino]-1-methyl-2-pyrrolecarboxamide 373362-34-6P, N-(3-Dimethylaminopropyl)-4-[[(4-amino-1-methyl-2-imidazolyl)carbonyl]amino]-1-methyl-2-pyrrolecarboxamide 373362-37-9P, N-(3-Dimethylaminopropyl)-4-[4-[[4-[[[4-amino-1-methyl-2-imidazolyl]carbonyl]amino]-1-methyl-2-imidazolyl]carbonyl]amino]-1-methyl-2-pyrrolecarboxamide
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of pyrrole-imidazole polyamide-duocarmycin conjugates as **DNA** interstrand crosslinking agents for treatment of cancer)

IT **373362-22-2P 373362-24-4P 373362-26-6P 373362-27-7P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of pyrrole-imidazole polyamide-duocarmycin conjugates as **DNA** interstrand crosslinking agents for treatment of cancer)

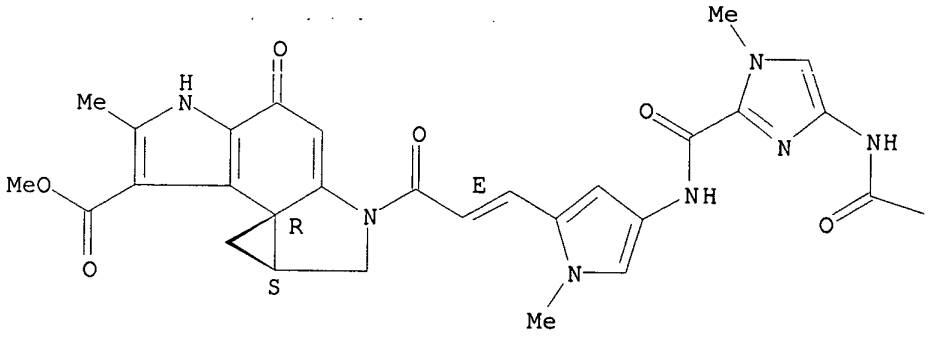
RN 373362-22-2 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-7-carboxylic acid, 2,2'-[(1,6-dioxo-1,6-hexanediyl)bis[imino(1-methyl-1H-imidazole-4,2-diyl)carbonylimino(1-methyl-1H-pyrrole-4,2-diyl)[(2E)-1-oxo-2-propene-3,1-diyl]]]bis[1,2,4,5,8,8a-hexahydro-6-methyl-4-oxo-, dimethyl ester, (7bR,7'bR,8aS,8'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

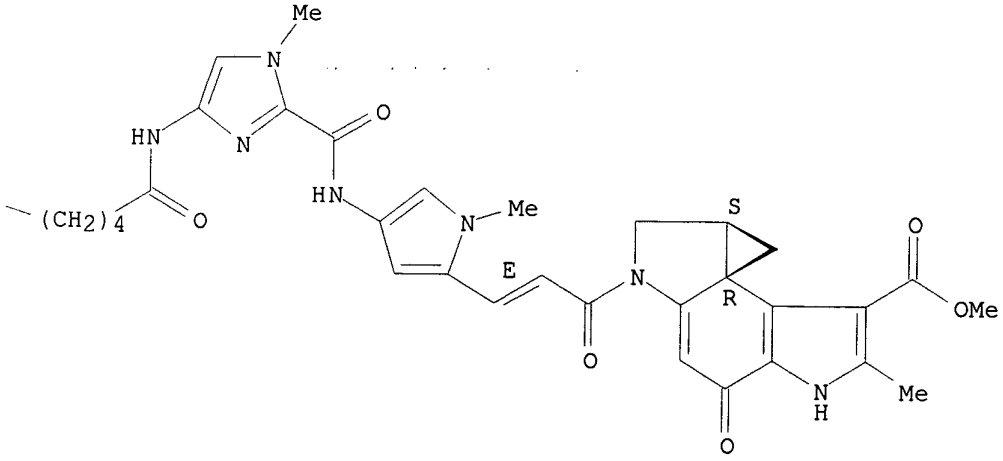
PAGE 1-A



PAGE 1-A



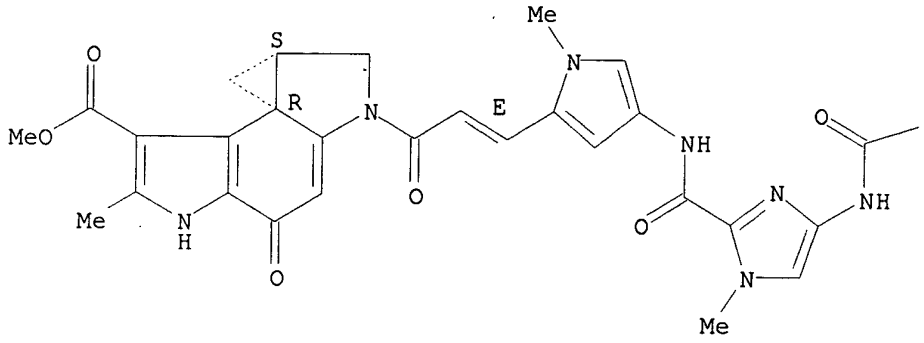
PAGE 1-B



RN 373362-24-4 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-7-carboxylic acid, 2,2'-[1,4-phenylenebis[carbonylimino(1-methyl-1H-imidazole-4,2-diyl)carbonylimino(1-methyl-1H-pyrrole-4,2-diyl)[(2E)-1-oxo-2-propene-3,1-diyl]]]bis[1,2,4,5,8,8a-hexahydro-6-methyl-4-oxo-, dimethyl ester, (7bR,7'bR,8aS,8'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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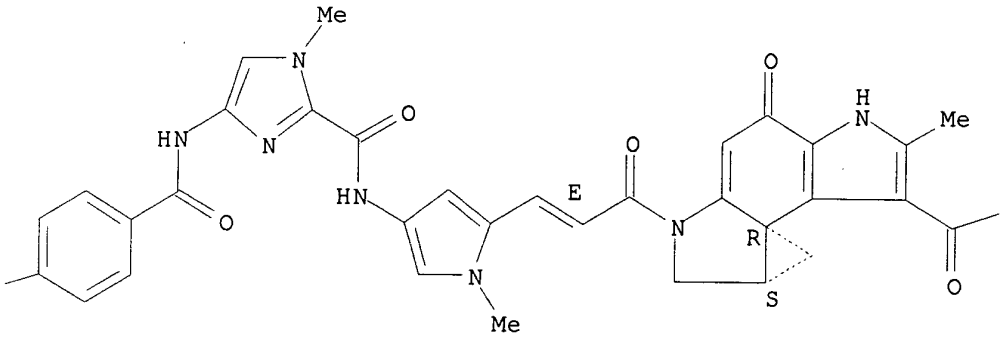


PAGE 1-C

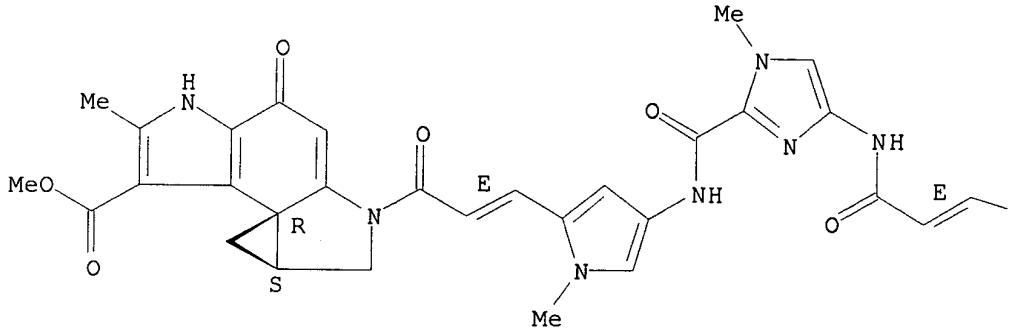
OMe

RN 373362-26-6 HCAPLUS

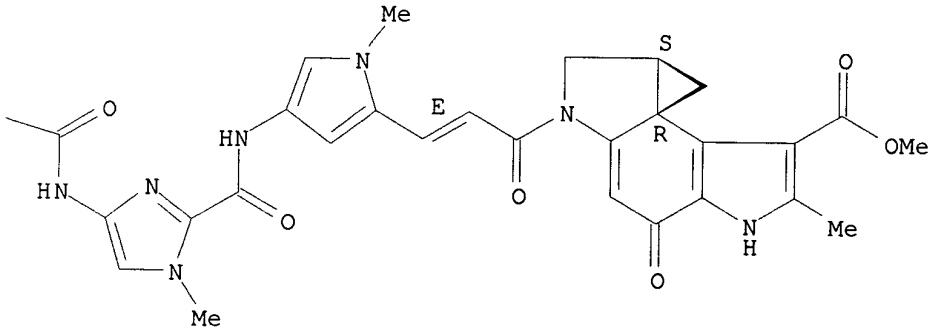
CN Cyclopropa[c]pyrrolo[3,2-e]indole-7-carboxylic acid, 2,2'-[(1,4-dioxo-2-butene-1,4-diyl)bis[imino(1-methyl-1H-imidazole-4,2-diyl)carbonylimino(1-methyl-1H-pyrrole-4,2-diyl)[(2E)-1-oxo-2-propene-3,1-diyl]]]bis[1,2,4,5,8,8a-hexahydro-6-methyl-4-oxo-, dimethyl ester, (7bR,7'bR,8aS,8'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



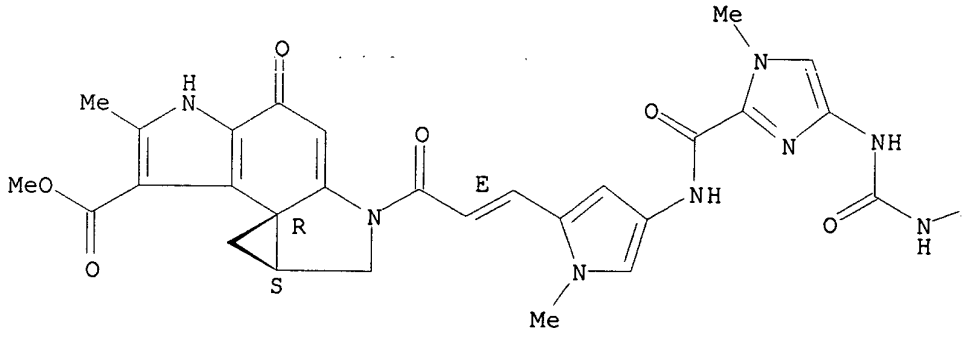
PAGE 1-B



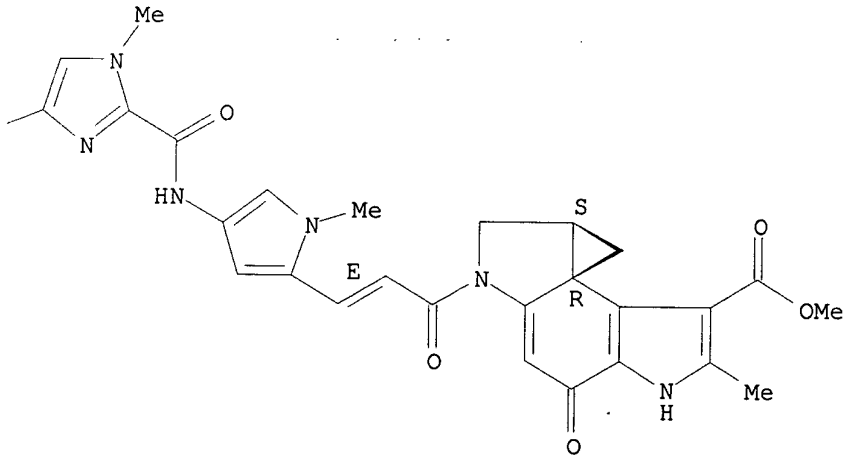
RN 373362-27-7 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-7-carboxylic acid, 2,2'-[carbonylbis[imino(1-methyl-1H-imidazole-4,2-diyl)carbonylimino(1-methyl-1H-pyrrole-4,2-diyl)[(2E)-1-oxo-2-propene-3,1-diyl]]]bis[1,2,4,5,8,8a-hexahydro-6-methyl-4-oxo-, dimethyl ester, (7bR,7'bR,8aS,8'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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ACCESSION NUMBER: 2001:365880 HCAPLUS
DOCUMENT NUMBER: 134:366795
TITLE: **DNA** sequence recognition by pyrrole-imidazole polyamide for use in anticancer drug screening
INVENTOR(S): Sugiyama, Hiroshi; Saito, Akira; Iida, Hirokazu
PATENT ASSIGNEE(S): Foundation for Scientific Technology Promotion, Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 14 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2001136974	A2	20010522	JP 1999-326007	19991116
WO 2001036677	A1	20010525	WO 2000-JP7992	20001113
W: US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				
EP 1152061	A1	20011107	EP 2000-974961	20001113
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
US 2003099998	A1	20030529	US 2002-285030	20021101

PRIORITY APPLN. INFO.:
JP 1999-326007 A 19991116
WO 2000-JP7992 W 20001113
US 2001-889379 A3 20010716

AB Novel chem. species represented by the following general formula B-L-A (B = a chem. structure capable of recognizing the base sequence of **DNA**, for example, optionally substituted pyrrole-imidazole polyamide; A = a chem. structure capable of binding to unnatural nucleotide bases, for example, the alkylation moiety of duocarmycin A; L = a linker capable of binding the chem. structures A and B, for example, vinyl) and use of those compds. in screening of biol. activity of chem. compds. are disclosed. Those compds. are preferably **DNA** alkylating agents, applicable as anticancer agents. Reagent kits for screening, including microtiter plates, are claimed. Drug screening using human cancer cell lines, CL-wt cells, HLC-2 cells, Jurkat cells, and HeLa cells, and synthetic scheme for the bioactive compds., are described.

IC ICM C12N015-09
ICS C12M001-26; C12Q001-68; C07D487-04

CC 27-10 (Heterocyclic Compounds (One Hetero Atom))
Section cross-reference(s): 1

ST **DNA** sequence recognition duocarmycin pyrrole imidazole polyamide conjugate; pyrrole imidazole polyamide **DNA** alkylating agent anticancer drug screening

IT Animal cell line
(CL-wt, drug screening in; **DNA** sequence recognition by pyrrole-imidazole polyamide for use in anticancer drug screening)

IT Alkylating agents, biological
Antitumor agents
Drug screening
Microtiter plates
(**DNA** sequence recognition by pyrrole-imidazole polyamide for use in anticancer drug screening)

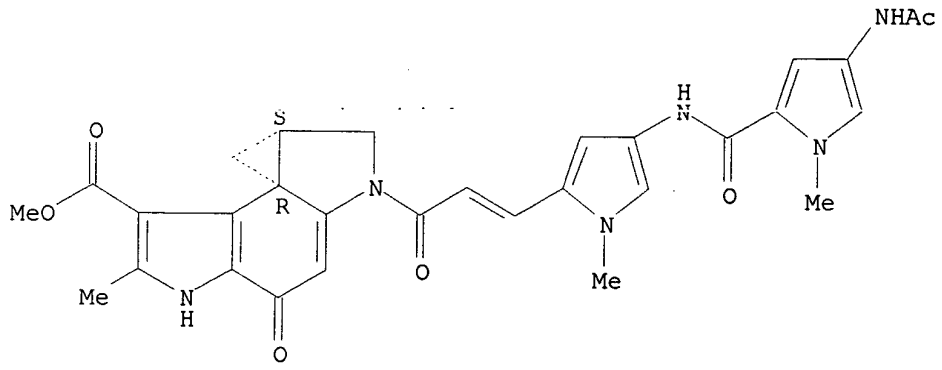
IT **Polyamides, properties**
RL: ARU (Analytical role, unclassified); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); PRP (Properties); ANST (Analytical study); BIOL (Biological study); PROC (Process); USES (Uses)
(**DNA** sequence recognition by pyrrole-imidazole polyamide for use in anticancer drug screening)

IT Animal cell line
(HLC-2, drug screening in; **DNA** sequence recognition by pyrrole-imidazole polyamide for use in anticancer drug screening)

IT Animal cell line
(JURKAT, drug screening in; **DNA** sequence recognition by pyrrole-imidazole polyamide for use in anticancer drug screening)

IT HeLa cell
(drug screening in; **DNA** sequence recognition by pyrrole-imidazole polyamide for use in anticancer drug screening)
IT Test kits
(for drug screening; **DNA** sequence recognition by pyrrole-imidazole polyamide for use in anticancer drug screening)
IT 109-97-7D, Pyrrole, deriv. 288-32-4D, Imidazole, deriv.
339984-88-2 339984-91-7
RL: ARU (Analytical role, unclassified); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); PRP (Properties); ANST (Analytical study); BIOL (Biological study); PROC (Process); USES (Uses)
(**DNA** sequence recognition by pyrrole-imidazole polyamide for use in anticancer drug screening)
IT **339984-92-8P**
RL: ARU (Analytical role, unclassified); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); PRP (Properties); SPN (Synthetic preparation); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(**DNA** sequence recognition by pyrrole-imidazole polyamide for use in anticancer drug screening)
IT 1192-58-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(**DNA** sequence recognition by pyrrole-imidazole polyamide for use in anticancer drug screening)
IT 18711-27-8P, 1-Methyl-4-nitro-pyrrole-2-carboxy aldehyde 339984-93-9P 339984-94-0P, Bis-pyrrole 339984-95-1P, Tris-pyrrole 339984-96-2DP, imidazole ester
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(**DNA** sequence recognition by pyrrole-imidazole polyamide for use in anticancer drug screening)
IT **339984-88-2 339984-91-7**
RL: ARU (Analytical role, unclassified); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); PRP (Properties); ANST (Analytical study); BIOL (Biological study); PROC (Process); USES (Uses)
(**DNA** sequence recognition by pyrrole-imidazole polyamide for use in anticancer drug screening)
RN 339984-88-2 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-7-carboxylic acid, 2-[3-[4-[[[4-(acetylamino)-1-methyl-1H-pyrrol-2-yl]carbonyl]amino]-1-methyl-1H-pyrrol-2-yl]-1-oxo-2-propenyl]-1,2,4,5,8,8a-hexahydro-6-methyl-4-oxo-, methyl ester, (7bR,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



RN 339984-91-7 HCAPLUS
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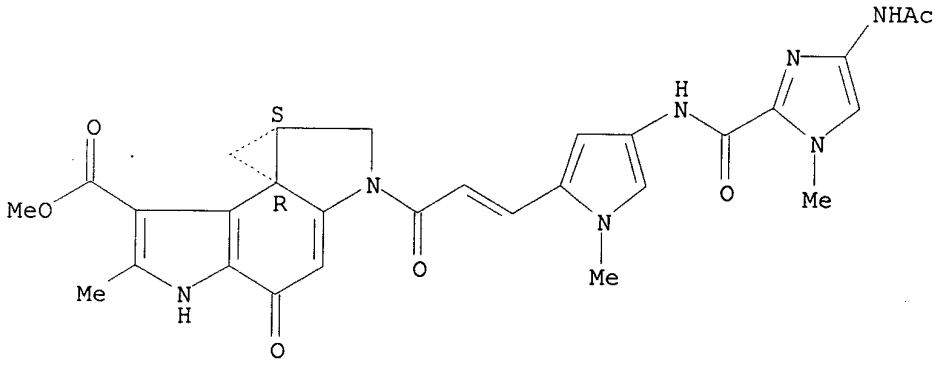
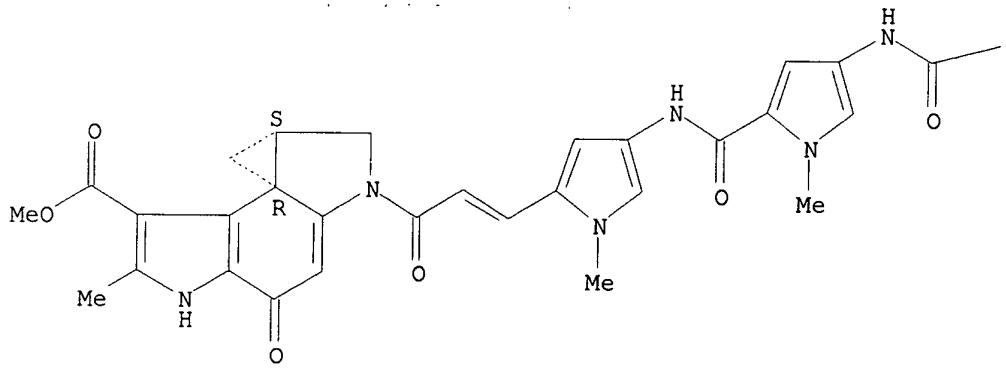
Absolute stereochemistry.
Double bond geometry unknown.



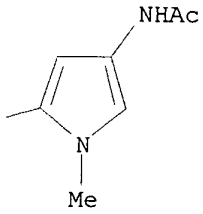
IT **339984-92-8P**
RL: ARU (Analytical role, unclassified); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); PRP (Properties); SPN (Synthetic preparation); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(**DNA** sequence recognition by pyrrole-imidazole polyamide for use in anticancer drug screening)
RN 339984-92-8 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-7-carboxylic acid, 2-[3-[4-[[[4-[[[4-(acetylamino)-1-methyl-1H-pyrrol-2-yl]carbonyl]amino]-1-methyl-1H-pyrrol-2-yl]carbonyl]amino]-1-methyl-1H-pyrrol-2-yl]-1-oxo-2-propenyl]-1,2,4,5,8,8a-hexahydro-6-methyl-4-oxo-, methyl ester, (7bR,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

PAGE 1-A



PAGE 1-B



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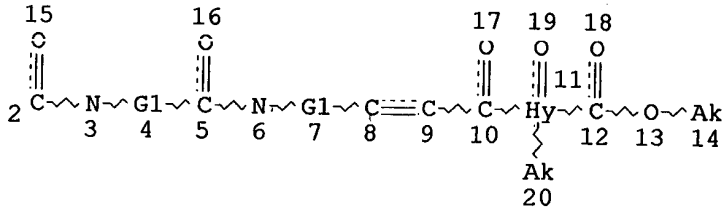


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CONNECT IS E1  RC AT  14
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GGCAT   IS PCY  AT  11
DEFAULT ECLEVEL IS LIMITED
ECOUNT  IS E11 C  E2 N  AT  11
ECOUNT  IS E4 C  E1 N  AT  21
ECOUNT  IS E3 C  E2 N  AT  22

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  21

STEREO ATTRIBUTES: NONE
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L47          10 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L46


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L47  ANSWER 1 OF 10  HCAPLUS  COPYRIGHT 2003 ACS
ACCESSION NUMBER:        2003:155388  HCAPLUS
DOCUMENT NUMBER:         138:333279
TITLE:                   Highly Efficient Sequence-Specific DNA Interstrand
                         Cross-Linking by Pyrrole/Imidazole CPI Conjugates
AUTHOR(S):               Bando, Toshikazu; Narita, Akihiko; Saito, Isao;
                         Sugiyama, Hiroshi
CORPORATE SOURCE:        Division of Biofunctional Molecules Institute of
                         Biomaterials and Bioengineering, Tokyo Medical and
                         Dental University, Tokyo, 101-0062, Japan
SOURCE:                  Journal of the American Chemical Society (2003),
                         125(12), 3471-3485
                         CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER:               American Chemical Society
DOCUMENT TYPE:           Journal
LANGUAGE:                English
AB   We have developed a novel type of DNA interstrand crosslinking agent by
     synthesizing dimers of a pyrrole (Py)/imidazole (Im)-diamide-CPI
     conjugate, ImPyLDu86, connected using seven different linkers.  The
     tetramethylene linker compd. [I], efficiently produces DNA interstrand
```

cross-links at the nine-base-pair sequence, 5'-PyGGC(T/A)GCCPu-3', only in the presence of a partner triamide, ImImPy. For efficient crosslinking by I with ImImPy, one A.cntdot.T base pair between two recognition sites was required to accommodate the linker region. Elimination of the A.cntdot.T base pair and insertion of an addnl. A.cntdot.T base pair and substitution with a G.cntdot.C base pair significantly reduced the degree of crosslinking. The sequence specificity of the interstrand crosslinking by I was also examd. in the presence of various triamides. The presence of ImImIm slightly reduced the formation of a cross-linked product compared to ImImPy. The mismatch partners, ImPyPy and PyImPy, did not produce an interstrand cross-link product with I, whereas ImPyPy and PyImPy induced efficient alkylation at their matching site with I. The interstrand crosslinking abilities of I were further examd. using denaturing PAGE with 5'-Texas Red-labeled 400- and 67-bp DNA fragments. The sequencing gel anal. of the 400-bp DNA fragment with ImImPy demonstrated that I alkylates several sites on the top and bottom strands, including one interstrand crosslinking match site, 5'-PyGGC(T/A)GCCPu-3'. To obtain direct evidence of interstrand cross-linkages on longer DNA fragments, a simple method using biotin-labeled complementary strands was developed, which produced a band corresponding to the interstrand cross-linked site on both top and bottom strands. Densitometric anal. indicated that the contribution of the interstrand cross-link in the obsd. alkylation bands was approx. 40%. This compd. efficiently cross-linked both strands at the target sequence. The present system consisted of a 1:2 complex of the alkylating agent and its partner ImImPy and caused an interstrand crosslinking in a sequence-specific fashion according to the base-pair recognition rule of Py-Im polyamides.

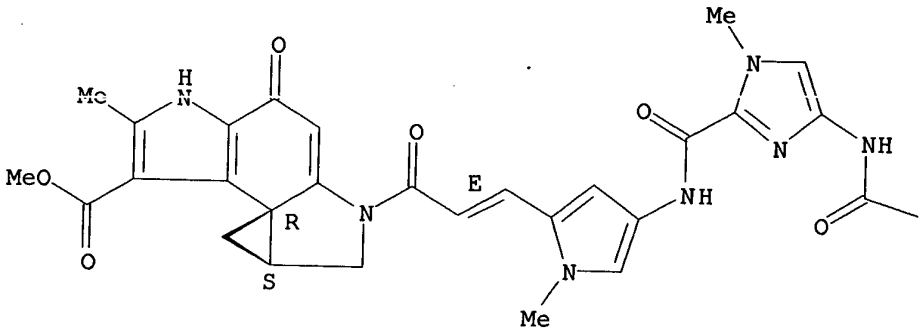
IT **373362-22-2P 373362-24-4P 373362-26-6P**
373362-27-7P 515867-58-0P 515867-60-4P
515867-62-6P
RL: BSU (Biological study, unclassified); BUU (Biological use, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(crosslinking; sequence-specific DNA interstrand crosslinking by pyrrole/imidazole CPI conjugates)

RN 373362-22-2 HCAPLUS

CN Cyclopropa[c]pyrrolo[3,2-e]indole-7-carboxylic acid, 2,2'-[(1,6-dioxo-1,6-hexanediyl)bis[imino(1-methyl-1H-imidazole-4,2-diyl)carbonylimino(1-methyl-1H-pyrrole-4,2-diyl)[(2E)-1-oxo-2-propene-3,1-diyl]]]bis[1,2,4,5,8,8a-hexahydro-6-methyl-4-oxo-, dimethyl ester, (7bR,7'bR,8aS,8'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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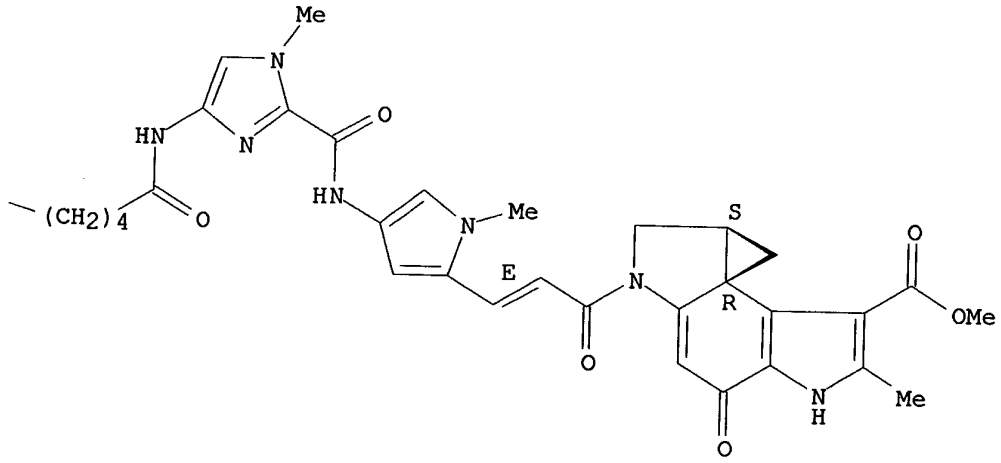

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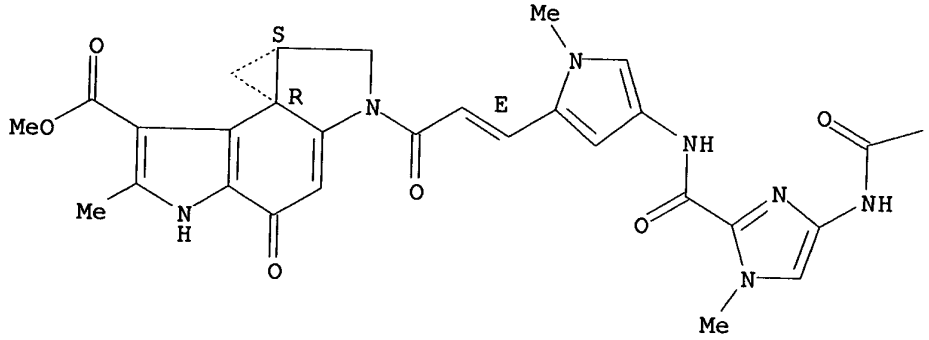
CN Cyclopropa[c]pyrrolo[3,2-e]indole-7-carboxylic acid, 2,2'-[1,4-phenylenebis[carbonylimino(1-methyl-1H-imidazole-4,2-diyl)carbonylimino(1-methyl-1H-pyrrole-4,2-diyl)[(2E)-1-oxo-2-propene-3,1-diyl]]]bis[1,2,4,5,8,8a-hexahydro-6-methyl-4-oxo-, dimethyl ester, (7bR,7'bR,8aS,8'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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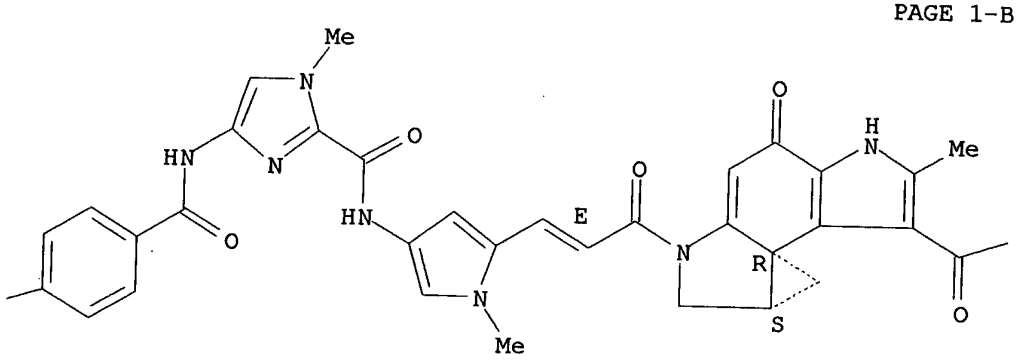

PAGE 1-C

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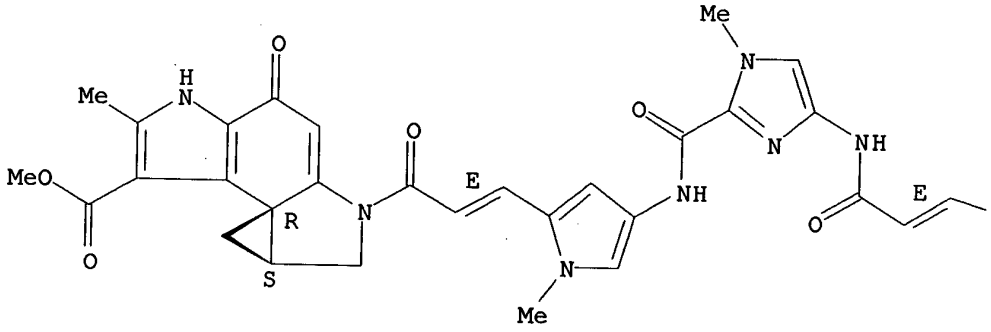
Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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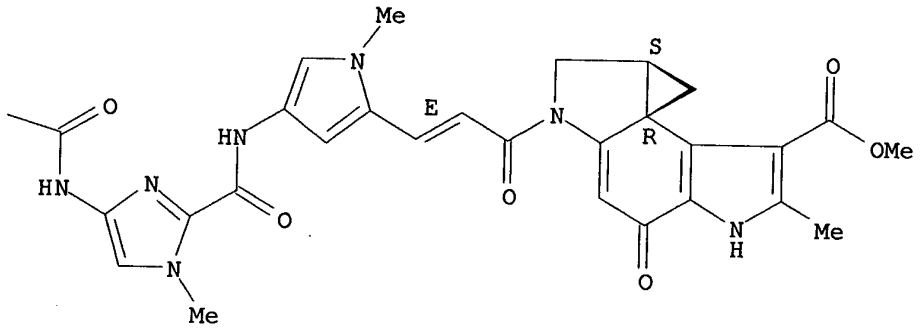

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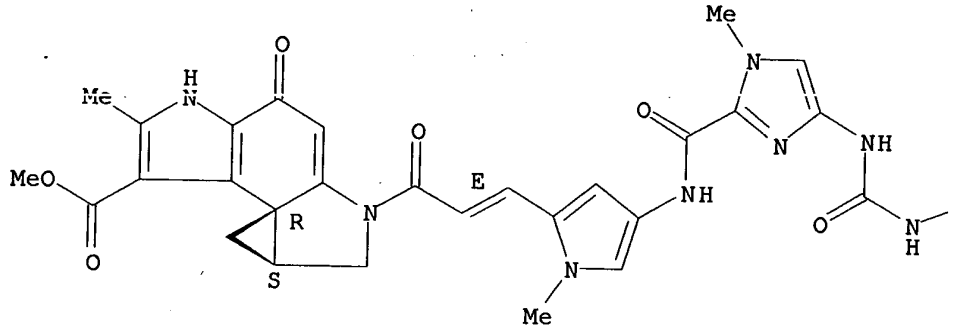
CN Cyclopropa[c]pyrrolo[3,2-e]indole-7-carboxylic acid, 2,2'-[carbonylbis[imino(1-methyl-1H-imidazole-4,2-diyl)carbonylimino(1-methyl-1H-pyrrole-4,2-diyl)[(2E)-1-oxo-2-propene-3,1-diyl]]]bis[1,2,4,5,8,8a-hexahydro-6-methyl-4-oxo-, dimethyl ester, (7bR,7'bR,8aS,8'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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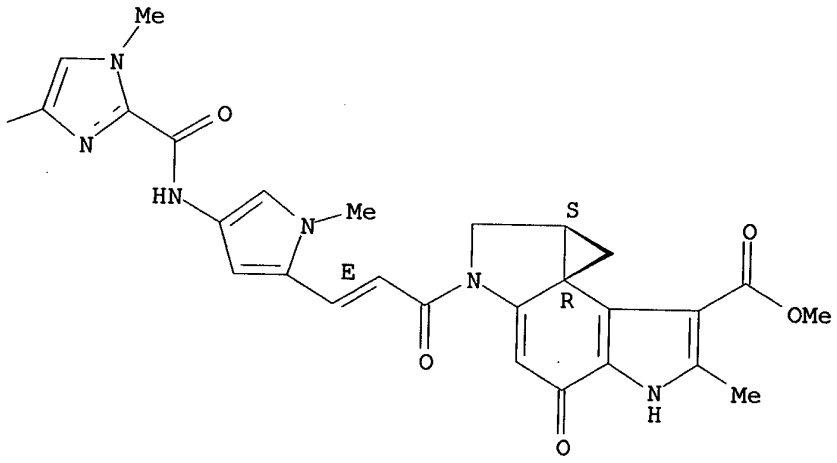

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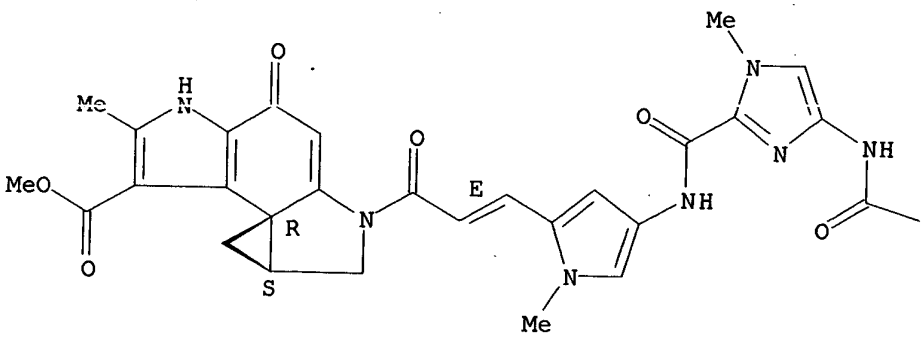
CN Cyclopropa[c]pyrrolo[3,2-e]indole-7-carboxylic acid, 2,2'-[(1,5-dioxo-1,5-pentanediyl)bis[imino(1-methyl-1H-imidazole-4,2-diyl)carbonylimino(1-methyl-1H-pyrrole-4,2-diyl)[(2E)-1-oxo-2-propene-3,1-diyl]]]bis[1,2,4,5,8,8a-hexahydro-6-methyl-4-oxo-, dimethyl ester, (7bR,7'bR,8aS,8'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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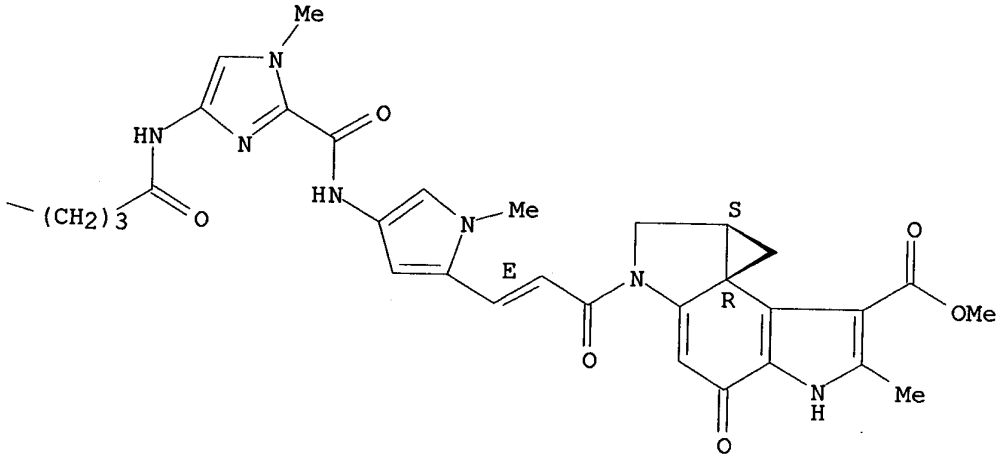

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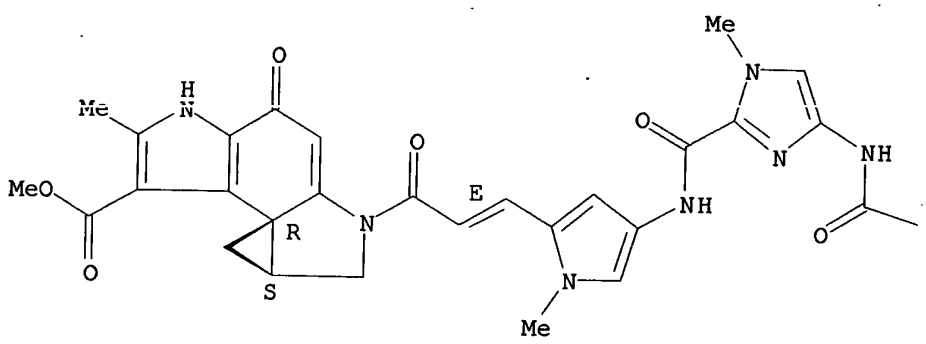
Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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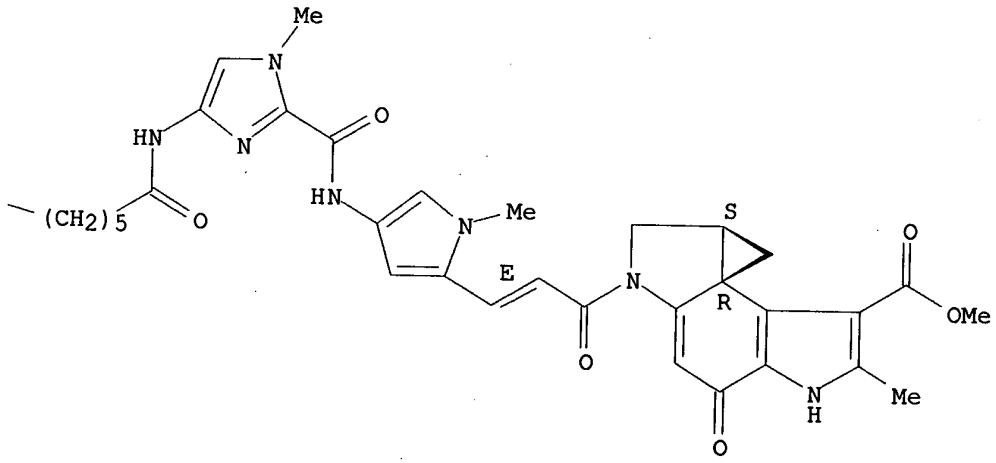
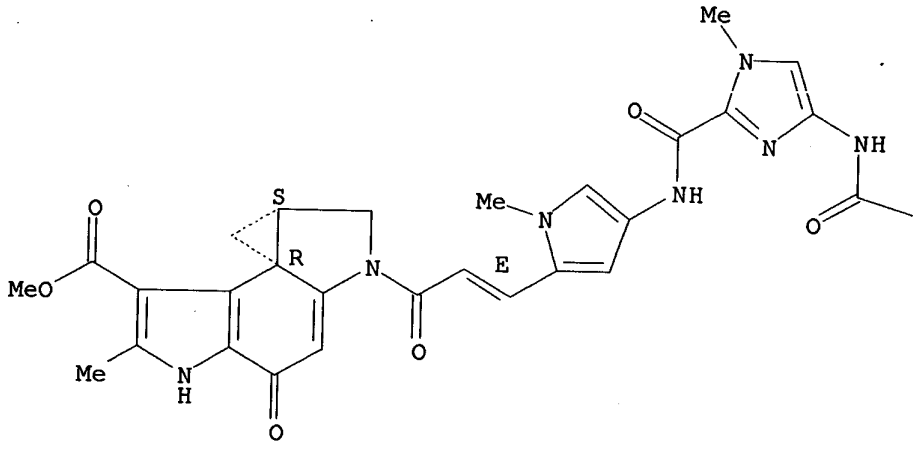


RN 515867-62-6 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-7-carboxylic acid, 2,2'-[1,3-phenylenebis[carbonylimino(1-methyl-1H-imidazole-4,2-diyl)carbonylimino(1-methyl-1H-pyrrole-4,2-diyl)[(2E)-1-oxo-2-propene-3,1-diyl]]]bis[1,2,4,5,8,8a-hexahydro-6-methyl-4-oxo-, dimethyl ester, (7bR,7'bR,8aS,8'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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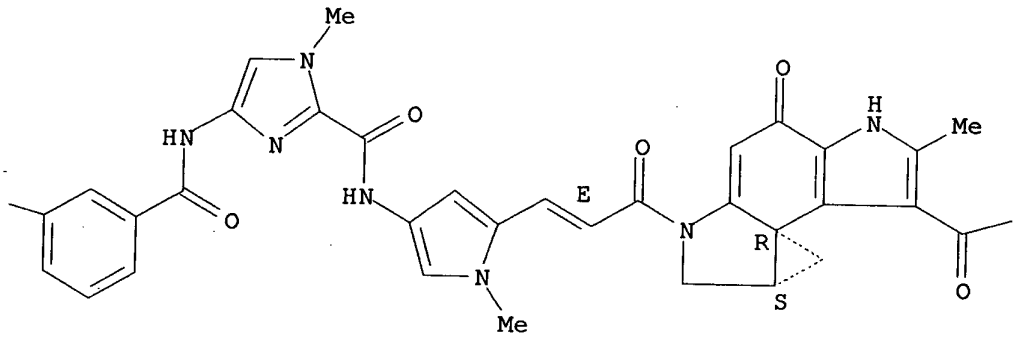

PAGE 1-C

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REFERENCE COUNT: 76 THERE ARE 76 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L47 ANSWER 2 OF 10 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:840303 HCAPLUS
DOCUMENT NUMBER: 138:132742
TITLE: Molecular design of a pyrrole - imidazole hairpin

polyamides for effective DNA alkylation

AUTHOR(S): Bando, Toshikazu; Narita, Akihiko; Saito, Isao; Sugiyama, Hiroshi

CORPORATE SOURCE: Division of Biofunctional Molecules Institute of Biomaterials and Bioengineering, Tokyo Medical and Dental University, Tokyo, 101-0062, Japan

SOURCE: Chemistry--A European Journal (2002), 8(20), 4781-4790
CODEN: CEUJED; ISSN: 0947-6539

PUBLISHER: Wiley-VCH Verlag GmbH & Co. KGaA

DOCUMENT TYPE: Journal

LANGUAGE: English

AB New hairpin polyamide-CPI (CPI = cyclopropylpyrroloindole) conjugates, compds. 12-14, were synthesized and their DNA-alkylating activities compared with the previously prepd. hairpin polyamide, compd. 1, by high-resoln. denaturing gel electrophoresis with 450 base pair (bp) DNA fragments and by HPLC product anal. of the synthetic decanucleotide. In accord with our previous results, alkylation by compd. 1 occurred predominantly at the G moiety of the sequence 5'-AGTCAG-3' (site 3). However, compd. 12, in which the structure of the alkylating moiety of compd. 1 is replaced with segment A of duocarmycin A DU-86 (CPI), did not show any DNA alkylating activity. In clear contrast, the hairpin CPI conjugate 13, which differs from compd. 1 in that it lacks one Py unit and possesses a vinyl linker, alkylated the A of 5'-AGTCAG-3' (site 3) efficiently at nanomolar concns. Alkylation by compd. 14, which has a vinyl linker, occurred at the A of 5'-AGTCCA-3' (site 6) and at several minor alkylation sites, including mismatch alkylation at A of 5'-TCACAA-3' (site 2). The significantly different reactivity of the alkylating hairpin polyamides 1, 12, 13, and 14 was further confirmed by HPLC product anal. by using a synthetic decanucleotide. The results suggest that hairpin polyamide-CPI conjugate 13 alkylates effectively according to Dervan's pairing rule, and with a new mode of recognition in which the Im-vinyl linker (L) pair targets G-C base pairs. These results demonstrate that incorporation of the vinyl-linker pairing with Im dramatically improves the reactivity of hairpin polyamide-CPI conjugates.

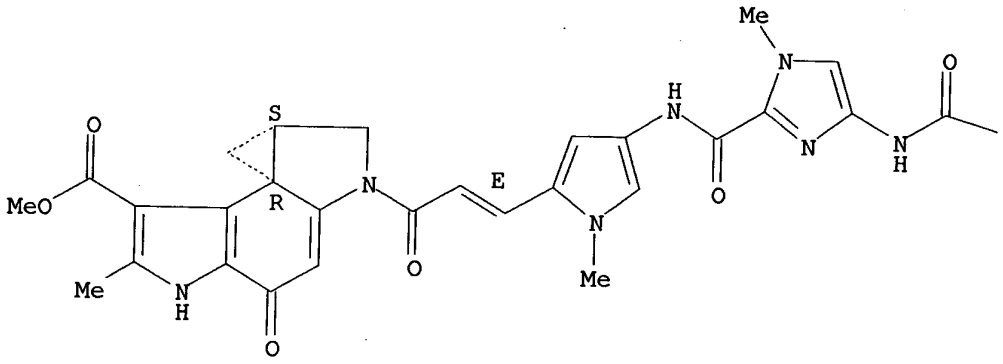
IT **491647-63-3P 491647-64-4P**
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(vinyl-linker pairing with imidazole in pyrrole - imidazole hairpin can improve polyamides for effective DNA alkylation)

RN 491647-63-3 HCAPLUS

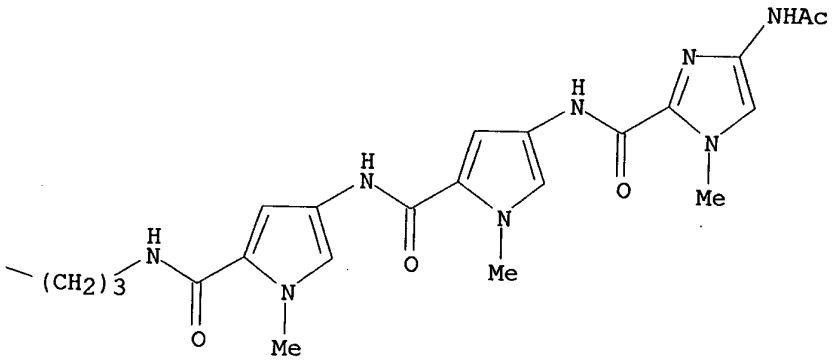
CN Cyclopropa[c]pyrrolo[3,2-e]indole-7-carboxylic acid, 2-[(2E)-3-[4-[[[4-[[4-[[[4-[[[4-[[[4-(acetylamino)-1-methyl-1H-imidazol-2-yl]carbonyl]amino]-1-methyl-1H-pyrrol-2-yl]carbonyl]amino]-1-methyl-1H-pyrrol-2-yl]carbonyl]amino]-1-oxobutyl]amino]-1-methyl-1H-imidazol-2-yl]carbonyl]amino]-1-methyl-1H-pyrrol-2-yl]-1-oxo-2-propenyl]-1,2,4,5,8,8a-hexahydro-6-methyl-4-oxo-, methyl ester, (7bR,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



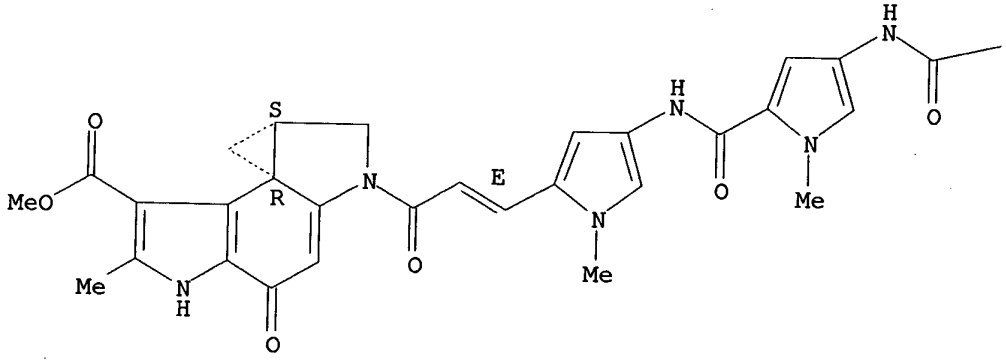
PAGE 1-B



RN 491647-64-4 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-7-carboxylic acid, 2-[(2E)-3-[4-[[[4-[[[4-[[4-[[[4-[[[4-[[[4-(acetylamino)-1-methyl-1H-imidazol-2-yl]carbonyl]amino]-1-methyl-1H-pyrrol-2-yl]carbonyl]amino]-1-methyl-1H-pyrrol-2-yl]carbonyl]amino]-1-oxobutyl]amino]-1-methyl-1H-imidazol-2-yl]carbonyl]amino]-1-methyl-1H-pyrrol-2-yl]carbonyl]amino]-1-methyl-1H-pyrrol-2-yl]-1-oxo-2-propenyl]-1,2,4,5,8,8a-hexahydro-6-methyl-4-oxo-, methyl ester, (7bR,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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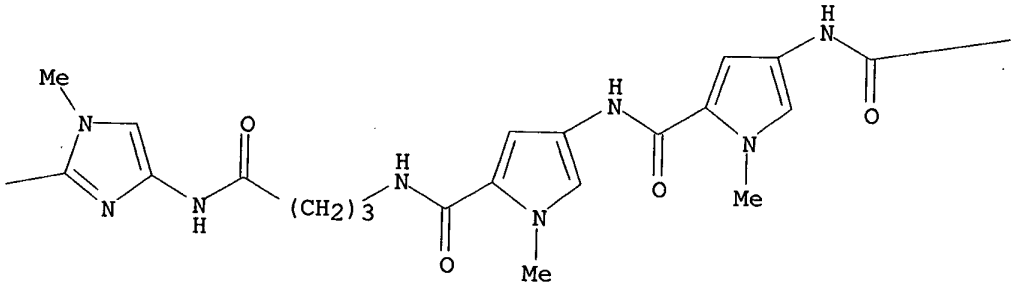

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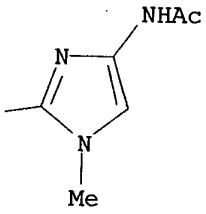


REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L47 ANSWER 3 OF 10 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2002:666652 HCAPLUS
DOCUMENT NUMBER: 138:85083
TITLE: Sequence-specific protection of plasmid DNA from restriction endonuclease hydrolysis by pyrrole-imidazole-cyclopropapyrroloindole conjugates
AUTHOR(S): Fujimoto, Kazuhisa; Iida, Hirokazu; Kawakami, Masako; Bando, Toshikazu; Tao, Zhi-Fu; Sugiyama, Hiroshi
CORPORATE SOURCE: Institute of Biomaterials and Bioengineering, Division of Biofunctional Molecules, Tokyo Medical and Dental University, Chiyoda, Tokyo, 101-0062, Japan
SOURCE: Nucleic Acids Research (2002), 30(17), 3748-3753
CODEN: NARHAD; ISSN: 0305-1048
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

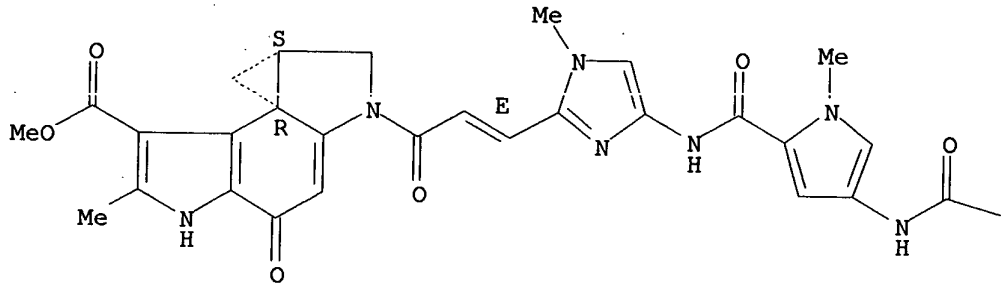
AB The pyrrole-imidazole (Py-Im) triamide-cyclopropa pyrroloindole (CPI) conjugates ImPyImLDu86 (7) and ImImPyLDu86 (14) were synthesized and their alkylating activities and inhibitory effects on DNA hydrolysis by restriction endonucleases were examd. Sequencing gel anal. demonstrated that conjugates 7 and 14 specifically alkylated DNA at 5'-CGCGCG-3' and 5'-PyGGCCPu-3', resp. Agarose gel electrophoresis indicated that incubation of a supercoiled plasmid, pSPORT I (4109 bp), with conjugate 7 effectively inhibited its hydrolysis by BssHII (5'-GCGCGC-3'), whereas conjugate 14 had no effect on this hydrolysis. These results suggest that conjugate 7 sequence-specifically inhibits the hydrolysis of DNA by BssHII. Sequence-specific alkylation by the Py-Im triamide-CPI conjugates was further confirmed by inhibition of the Eco52I (5'-CGGCCG-3') hydrolysis of conjugate 14-treated pQBI PGK (5387 bp). In clear contrast, hydrolysis of pQB1 PGK by DraI (3'-TTTAAA-3') was not inhibited by 5 .mu.M conjugate 14. That ImImPy did not inhibit the hydrolysis of pQB1 PGK indicates that covalent bond formation is necessary for inhibition. A similar expt., using linear pQBI PGK, achieved the same extent of protection of the DNA with approx. half the concn. of conjugate 14 as was required to protect supercoiled DNA from hydrolysis.

IT **484017-85-8P 484017-86-9P**
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(sequence-specific protection of plasmid DNA from restriction endonuclease hydrolysis by pyrrole-imidazole-cyclopropapyrroloindole conjugates)

RN 484017-85-8 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-7-carboxylic acid, 2-[(2E)-3-[4-[[[4-[[[4-(acetylamino)-1-methyl-1H-imidazol-2-yl]carbonyl]amino]-1-methyl-1H-pyrrol-2-yl]carbonyl]amino]-1-methyl-1H-imidazol-2-yl]-1-oxo-2-propenyl]-1,2,4,5,8,8a-hexahydro-6-methyl-4-oxo-, methyl ester, (7bR,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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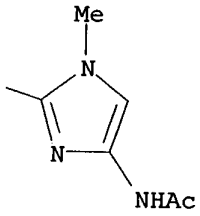
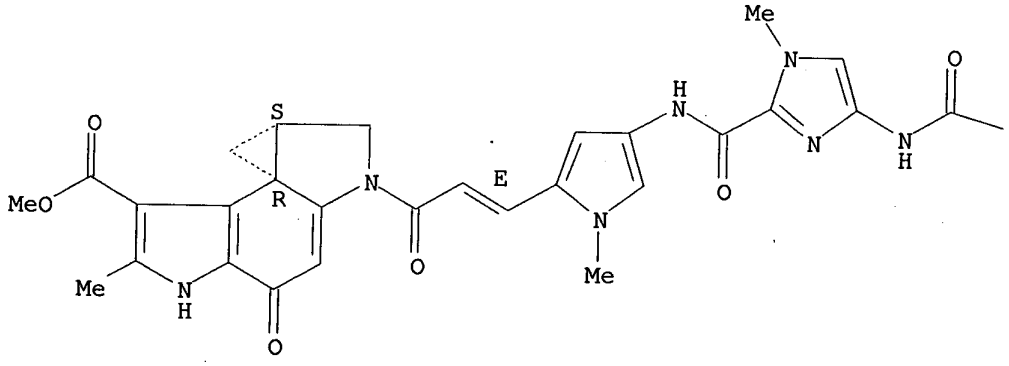


RN 484017-86-9 HCAPLUS

CN Cyclopropa[c]pyrrolo[3,2-e]indole-7-carboxylic acid, 2-[(2E)-3-[4-[[[4-[[[4-(acetylamino)-1-methyl-1H-imidazol-2-yl]carbonyl]amino]-1-methyl-1H-imidazol-2-yl]carbonyl]amino]-1-methyl-1H-pyrrol-2-yl]-1-oxo-2-propenyl]-1,2,4,5,8,8a-hexahydro-6-methyl-4-oxo-, methyl ester, (7bR,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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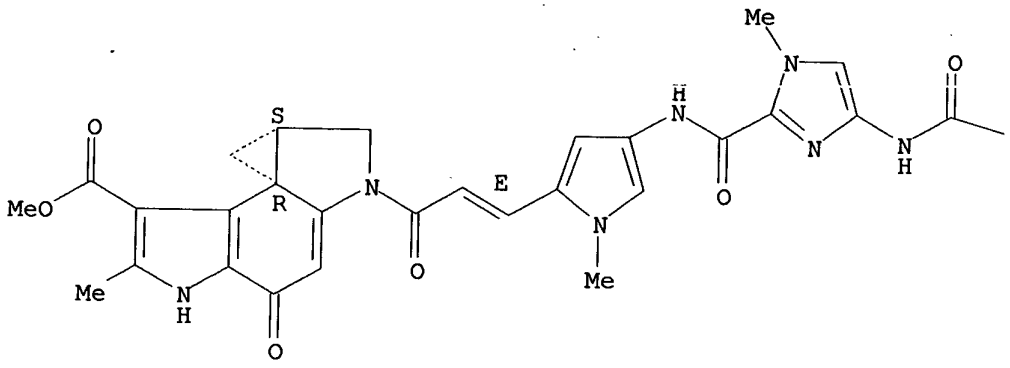

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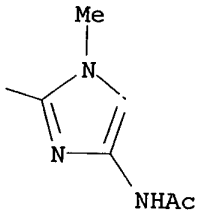


REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L47 ANSWER 4 OF 10 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:833321 HCAPLUS
DOCUMENT NUMBER: 135:371743
TITLE: Preparation of pyrrole-imidazole polyamide-duocarmycin segment conjugates as interstrand crosslinking agents for DNA in cancer treatment
INVENTOR(S): Sugiyama, Hiroshi; Bando, Toshikazu; Iida, Hirokazu; Saito, Isao
PATENT ASSIGNEE(S): Japan Science and Technology Corporation, Japan
SOURCE: PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001085733	A1	20011115	WO 2001-JP3756	20010501

W: US
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR

JP 2001322992 A2 20011120 JP 2000-140361 20000512
EP 1281711 A1 20030205 EP 2001-926081 20010501
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY, TR
PRIORITY APPLN. INFO.: JP 2000-140361 A 20000512
WO 2001-JP3756 W 20010501
OTHER SOURCE(S): MARPAT 135:371743
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Compds. represented by the following general formula A-L-B-X-B-L-A (I; wherein B represents a chem. structure capable of recognizing a base sequence of a DNA; A represents a chem. structure capable of binding to one of the bases of the DNA; L represents a linker by which the chem. structures A and B can be linked to each other; and X represents a spacer by which the A-L-B components can be linked to each other), by which two DNA strands can be interstrand-crosslinked, are prepd. Also claimed are a method of interstrand-crosslinking DNA by using these compds. and medicinal compns. contg. interstrand crosslinking agents of DNA. In the compds. I, the above chem. structure capable of recognizing a base sequence of a DNA is derived from pyrrole and/or imidazole and the chem. structure capable of binding to one of the bases of the DNA possesses a cyclopropane ring. More specifically, the compds. represented by N-[3-[4-(N-methylimidazol-2-ylcarbonylamino)-N-methylpyrrol-2-yl]acryloyl]cyclopropa[c]pyrrolo[3,2-e]indole derivs. (pyrrole-imidazole polyamide-duocarmycin segment conjugates) [II; X = CO, COCH:CHCO, CO(CH2)4CO, CO-p-C6H4-CO] are prepd. The B component in the compds. I, i.e. the 4-(N-methylimidazol-2-ylcarbonylamino)-N-methylpyrrole moiety of II, recognizes a DNA base sequence and is capable of specifically interstrand-crosslinking to the specific base sequence of DNA. These compds. inhibit the replication of DNA by interstrand-crosslinking to DNA and thereby are useful for the treatment of cancer. Interstrand-crosslinking reaction of the compds. II to DNA oligomers was examd. using polyacrylamide gel electrophoresis. For example, it was confirmed that II [X = CO(CH2)4CO] interstrand-crosslinked to the TGGC or GCCA or its complimentary sequence of DNA, in particular in the copresence of a triamide (III; X = Y = N and Z = CH; X = Y = Z = N; X = N and Y = Z = CH; X = Z = CH and Y = N).

IT **373362-22-2P 373362-24-4P 373362-26-6P 373362-27-7P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of pyrrole-imidazole polyamide-duocarmycin conjugates as DNA interstrand crosslinking agents for treatment of cancer)

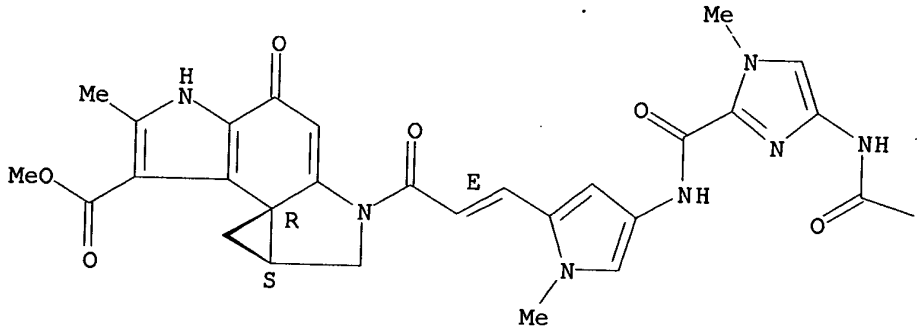
RN 373362-22-2 HCAPLUS

CN Cyclopropa[c]pyrrolo[3,2-e]indole-7-carboxylic acid, 2,2'-[(1,6-dioxo-1,6-hexanediyl)bis[imino(1-methyl-1H-imidazole-4,2-diyl)carbonylimino(1-methyl-1H-pyrrole-4,2-diyl)[(2E)-1-oxo-2-propene-3,1-diyl]]]bis[1,2,4,5,8,8a-hexahydro-6-methyl-4-oxo-, dimethyl ester, (7bR,7'bR,8aS,8'aS)- (9CI) (CA INDEX NAME)

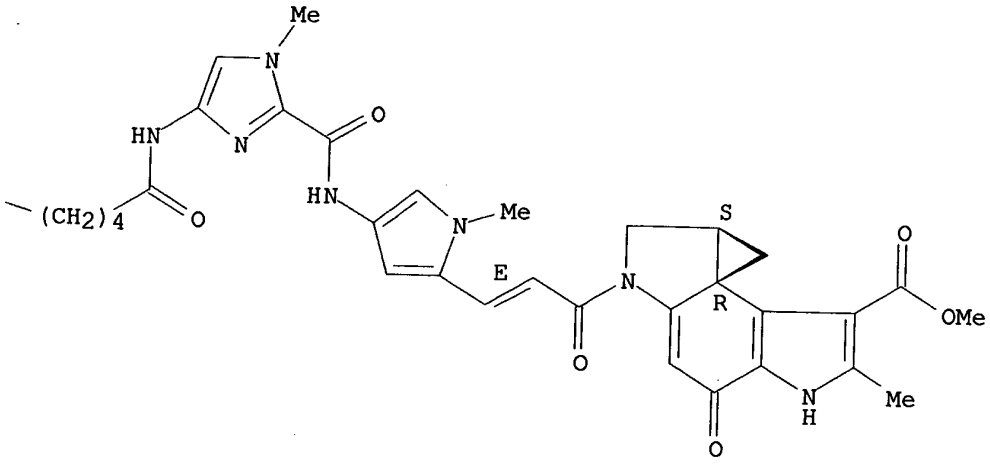
Absolute stereochemistry.

Double bond geometry as shown.

PAGE 1-A



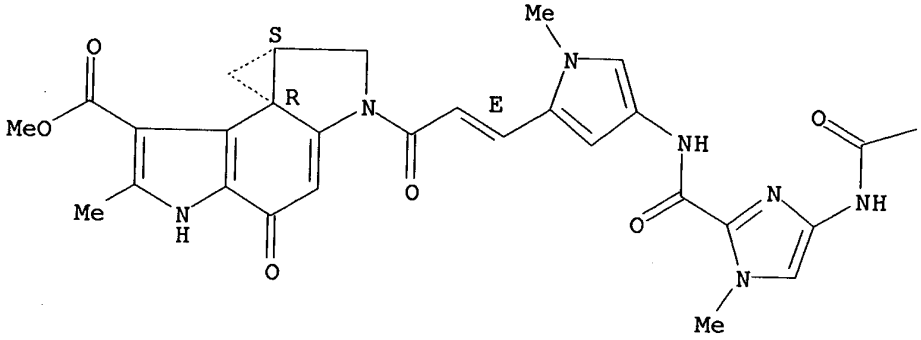
PAGE 1-B



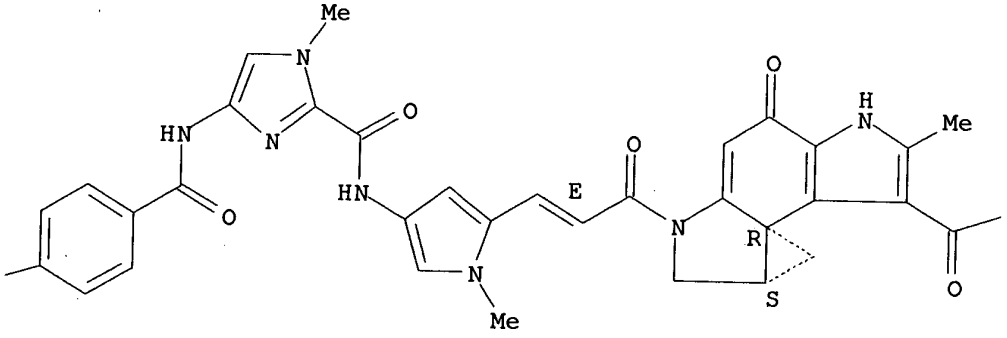
RN 373362-24-4 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-7-carboxylic acid, 2,2'-[1,4-phenylenebis[carbonylimino(1-methyl-1H-imidazole-4,2-diyl)carbonylimino(1-methyl-1H-pyrrole-4,2-diyl)[(2E)-1-oxo-2-propene-3,1-diyl]]]bis[1,2,4,5,8,8a-hexahydro-6-methyl-4-oxo-, dimethyl ester, (7bR,7'bR,8aS,8'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



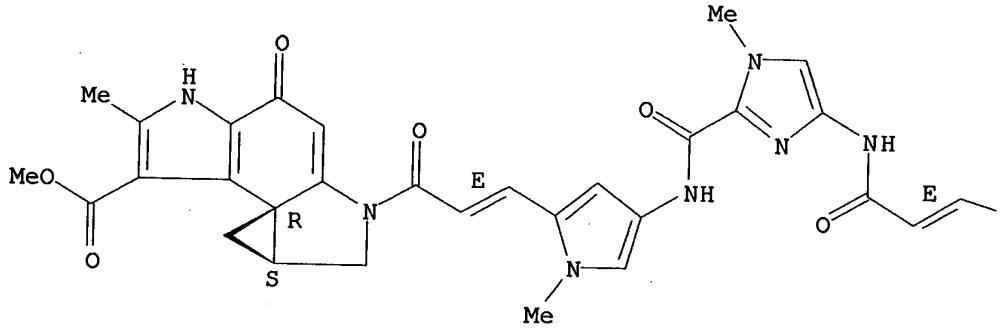
PAGE 1-C

—OMe

RN 373362-26-6 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-7-carboxylic acid, 2,2'-[(1,4-dioxo-2-butene-1,4-diyl)bis[imino(1-methyl-1H-imidazole-4,2-diyl)carbonylimino(1-methyl-1H-pyrrole-4,2-diyl)[(2E)-1-oxo-2-propene-3,1-diyl]]]bis[1,2,4,5,8,8a-hexahydro-6-methyl-4-oxo-, dimethyl ester, (7bR,7'bR,8aS,8'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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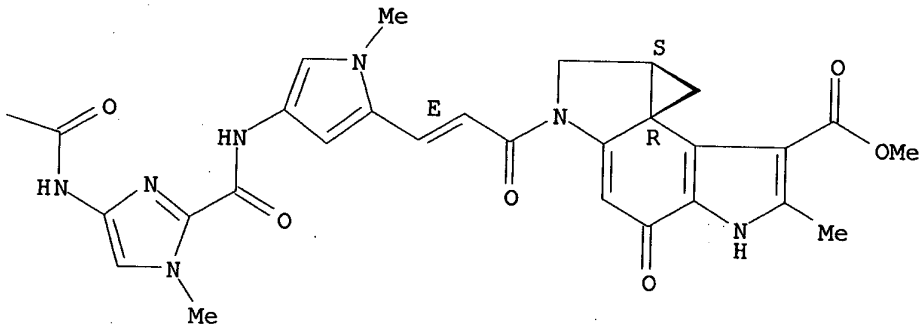
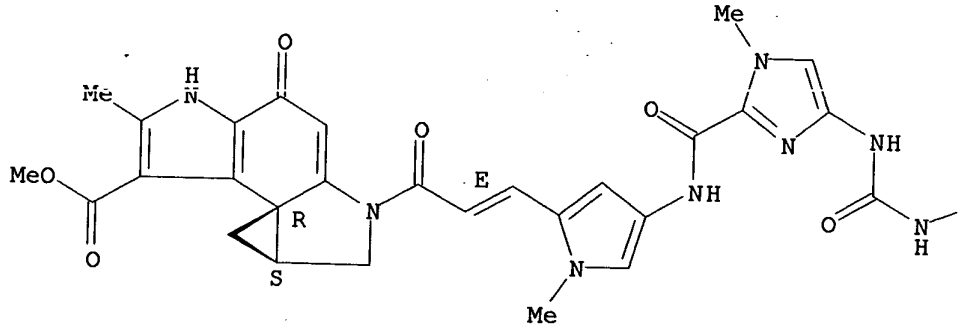


RN 373362-27-7 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-7-carboxylic acid, 2,2'-[carbonylbis[imino(1-methyl-1H-imidazole-4,2-diyl)carbonylimino(1-methyl-1H-pyrrole-4,2-diyl)[(2E)-1-oxo-2-propene-3,1-diyl]]]bis[1,2,4,5,8,8a-hexahydro-6-methyl-4-oxo-, dimethyl ester, (7bR,7'bR,8aS,8'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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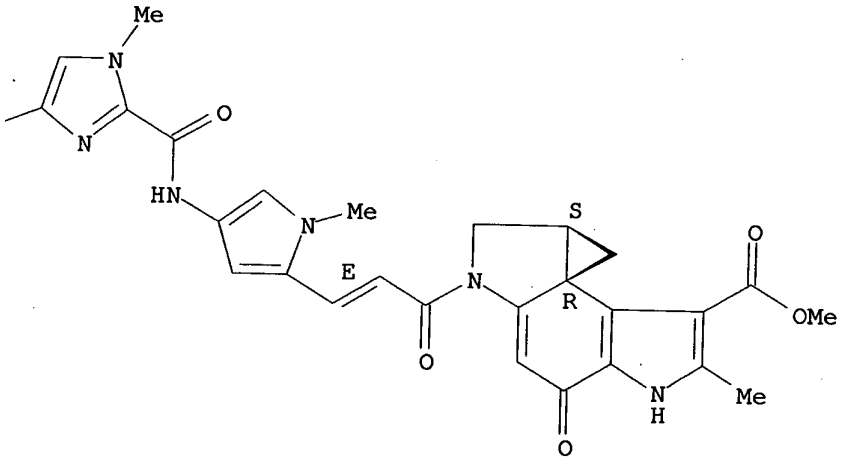


REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L47 ANSWER 5 OF 10 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:365880 HCAPLUS
DOCUMENT NUMBER: 134:366795
TITLE: DNA sequence recognition by pyrrole-imidazole polyamide for use in anticancer drug screening
INVENTOR(S): Sugiyama, Hiroshi; Saito, Akira; Iida, Hirokazu
PATENT ASSIGNEE(S): Foundation for Scientific Technology Promotion, Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 14 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2001136974	A2	20010522	JP 1999-326007	19991116
WO 2001036677	A1	20010525	WO 2000-JP7992	20001113
W: US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				
EP 1152061	A1	20011107	EP 2000-974961	20001113
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
US 2003099998	A1	20030529	US 2002-285030	20021101

PRIORITY APPLN. INFO.:
JP 1999-326007 A 19991116
WO 2000-JP7992 W 20001113
US 2001-889379 A3 20010716

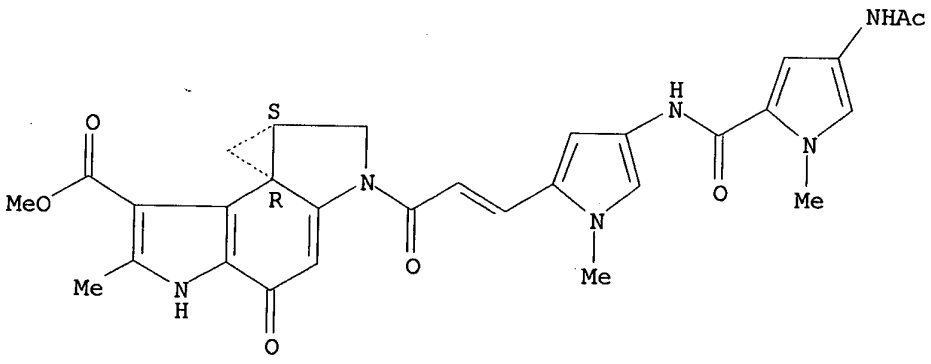
AB Novel chem. species represented by the following general formula B-L-A (B = a chem. structure capable of recognizing the base sequence of DNA, for example, optionally substituted pyrrole-imidazole polyamide; A = a chem. structure capable of binding to unnatural nucleotide bases, for example, the alkylation moiety of duocarmycin A; L = a linker capable of binding the chem. structures A and B, for example, vinyl) and use of those compds. in screening of biol. activity of chem. compds. are disclosed. Those compds. are preferably DNA alkylating agents, applicable as anticancer agents. Reagent kits for screening, including microtiter plates, are claimed. Drug screening using human cancer cell lines, CL-wt cells, HLC-2 cells, Jurkat cells, and HeLa cells, and synthetic scheme for the bioactive compds., are described.

JT **339984-88-2 339984-91-7**
RL: ARU (Analytical role, unclassified); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); PRP (Properties); ANST (Analytical study); BIOL (Biological study); PROC (Process); USES (Uses)
(DNA sequence recognition by pyrrole-imidazole polyamide for use in anticancer drug screening)

RN 339984-88-2 HCAPLUS

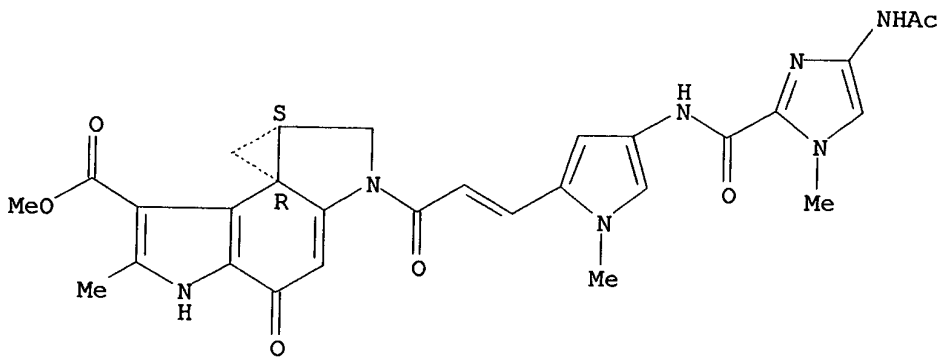
CN Cyclopropa[c]pyrrolo[3,2-e]indole-7-carboxylic acid, 2-[3-[4-[[[4-(acetylamino)-1-methyl-1H-pyrrol-2-yl]carbonyl]amino]-1-methyl-1H-pyrrol-2-yl]-1-oxo-2-propenyl]-1,2,4,5,8,8a-hexahydro-6-methyl-4-oxo-, methyl ester, (7bR,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.



RN 339984-91-7 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-7-carboxylic acid, 2-[3-[4-[[[4-(acetylamino)-1-methyl-1H-imidazol-2-yl]carbonyl]amino]-1-methyl-1H-pyrrol-2-yl]-1-oxo-2-propenyl]-1,2,4,5,8,8a-hexahydro-6-methyl-4-oxo-, methyl ester, (7bR,8aS)- (9CI) (CA INDEX NAME)

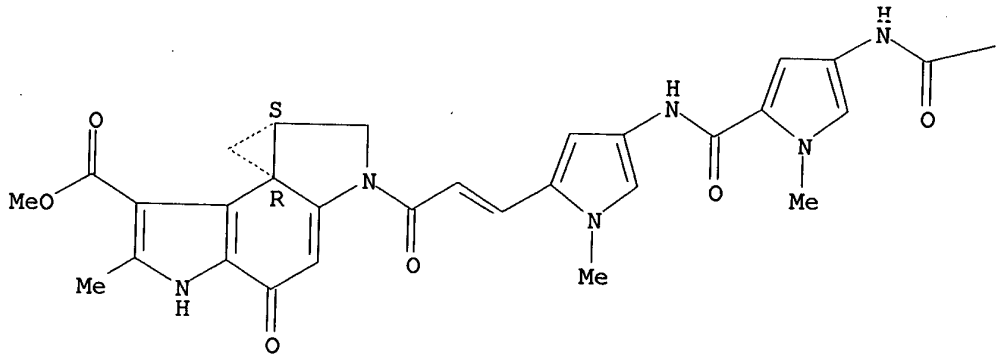
Absolute stereochemistry.
Double bond geometry unknown.



IT **339984-92-8P**
RL: ARU (Analytical role, unclassified); BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BUU (Biological use, unclassified); PRP (Properties); SPN (Synthetic preparation); ANST (Analytical study); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(DNA sequence recognition by pyrrole-imidazole polyamide for use in anticancer drug screening)
RN 339984-92-8 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-7-carboxylic acid, 2-[3-[4-[[[4-[[[4-(acetylamino)-1-methyl-1H-pyrrol-2-yl]carbonyl]amino]-1-methyl-1H-pyrrol-2-yl]carbonyl]amino]-1-methyl-1H-pyrrol-2-yl]-1-oxo-2-propenyl]-1,2,4,5,8,8a-hexahydro-6-methyl-4-oxo-, methyl ester, (7bR,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

PAGE 1-A



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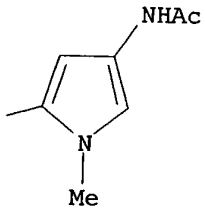


L47 ANSWER 6 OF 10 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:327062 HCAPLUS
DOCUMENT NUMBER: 135:102536
TITLE: Sequence-specific DNA interstrand cross-linking by imidazole-pyrrole CPI conjugate
AUTHOR(S): Bando, Toshikazu; Iida, Hirokazu; Saito, Isao; Sugiyama, Hiroshi
CORPORATE SOURCE: CREST Japan Science and Technology Corporation (JST) Japan Division of Biofunctional Molecules Institute of Biomaterials and Bioengineering Tokyo Medical and Dental University, Kanda Chiyoda Tokyo, 101-0062, Japan
SOURCE: Journal of the American Chemical Society (2001), 123(21), 5158-5159
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB DNA interstrand crosslinking inhibits both DNA replication and gene expression and therefore has considerable potential for mol. biol. and human medicine. However, an interstrand crosslinking agent that targets a predetd. base-pair sequence has not been achieved. Minor-groove binding polyamides that contain N-methylimidazole (Im)-N-methylpyrrole

(Py)hydroxypyrrole (Hp), which uniquely recognize each of the four Watson-Crick base pairs, can be used as novel recognition parts of sequence-specific DNA alkylating agents. We also demonstrated that Im/Py diamide-CPI conjugate with a vinyl linker, ImPyLDu86, alkylates double-stranded DNA at predetd. sequences through highly cooperative homodimer formation. Herein we describe the synthesis of a covalent dimer of ImPyLDu86 connected with various linkers and their DNA interstrand crosslinking abilities. In conclusion, we developed a novel DNA interstrand crosslinking agent, that crosslinked double strands only in the presence of ImImPy at a nine-base-pair sequence, 5'-PyGGC(T/A)GCCPu-3'. The present system will provide a promising approach for the design of novel sequence-specific DNA interstrand crosslinking agents. Targeting specific sequences in the human genome by such sequence-specific crosslinking agent would constitute a powerful gene-regulating tool. Further studies on the applicability of this novel class of crosslinking agents are currently in progress.

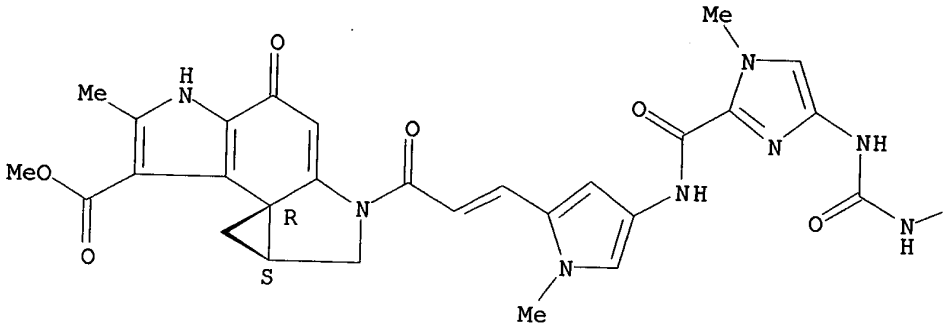
IT **349647-78-5 349647-79-6 349647-80-9 349647-82-1 349647-83-2**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(sequence-specific DNA interstrand crosslinking by imidazole-pyrrole CPI conjugate)

RN 349647-78-5 HCAPLUS

CN Cyclopropa[c]pyrrolo[3,2-e]indole-7-carboxylic acid, 2,2'-[carbonylbis[imino(1-methyl-1H-imidazole-4,2-diyl)carbonylimino(1-methyl-1H-pyrrole-4,2-diyl)(1-oxo-2-propene-3,1-diyl)]]bis[1,2,4,5,8,8a-hexahydro-6-methyl-4-oxo-, dimethyl ester, (7bR,7'bR,8aS,8'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

PAGE 1-A



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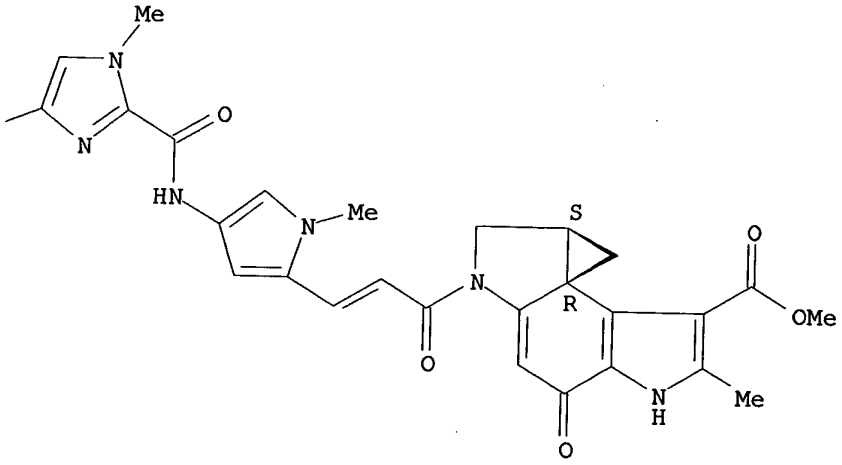
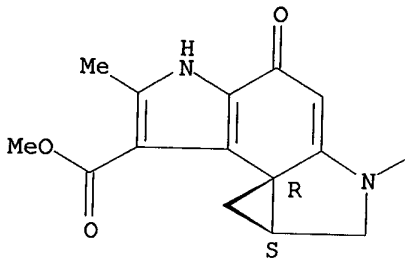


RN 349647-79-6 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-7-carboxylic acid, 2,2'-[(1,4-dioxo-2-butene-1,4-diyl)bis[imino(1-methyl-1H-imidazole-4,2-diyl)carbonylimino(1-methyl-1H-pyrrole-4,2-diyl)(1-oxo-2-propene-3,1-diyl)]]bis[1,2,4,5,8,8a-hexahydro-6-methyl-4-oxo-, dimethyl ester, (7bR,7'bR,8aS,8'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

PAGE 1-A



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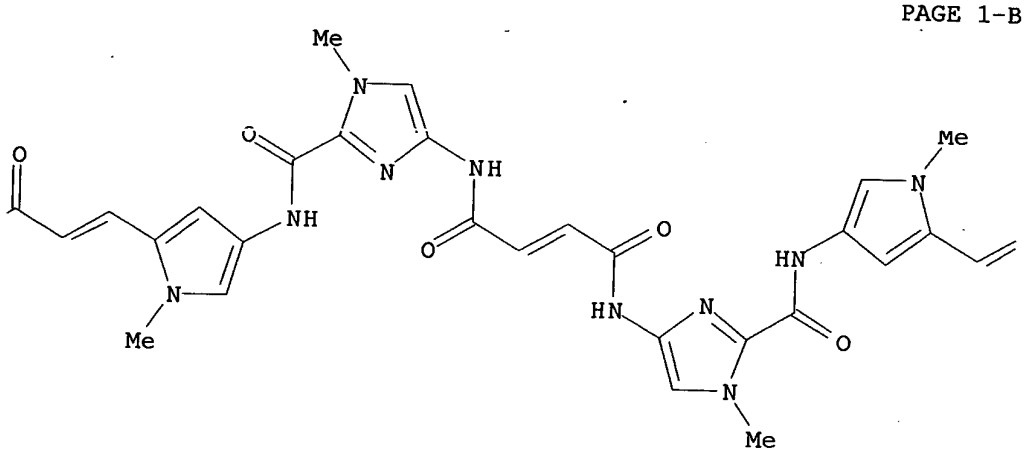

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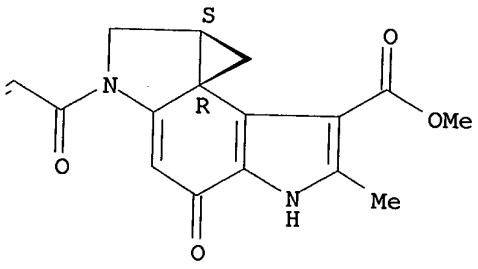
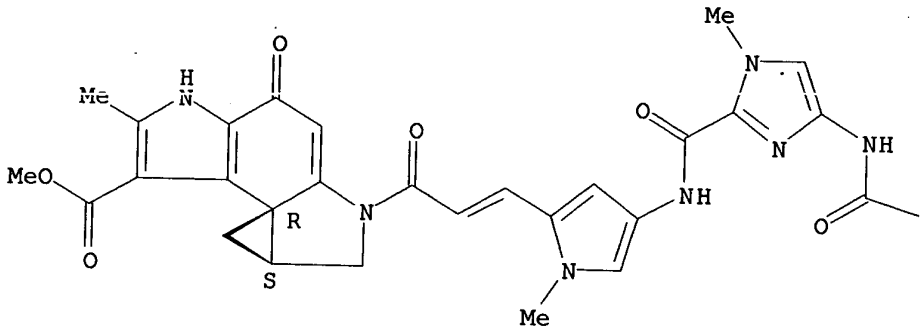


RN 349647-80-9 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-7-carboxylic acid, 2,2'-[(1,5-dioxo-1,5-pentanediyl)bis[imino(1-methyl-1H-imidazole-4,2-diyl)carbonylimino(1-methyl-1H-pyrrole-4,2-diyl)(1-oxo-2-propene-3,1-diyl)]]bis[1,2,4,5,8,8a-hexahydro-6-methyl-4-oxo-, dimethyl ester, (7bR,7'bR,8aS,8'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

PAGE 1-A



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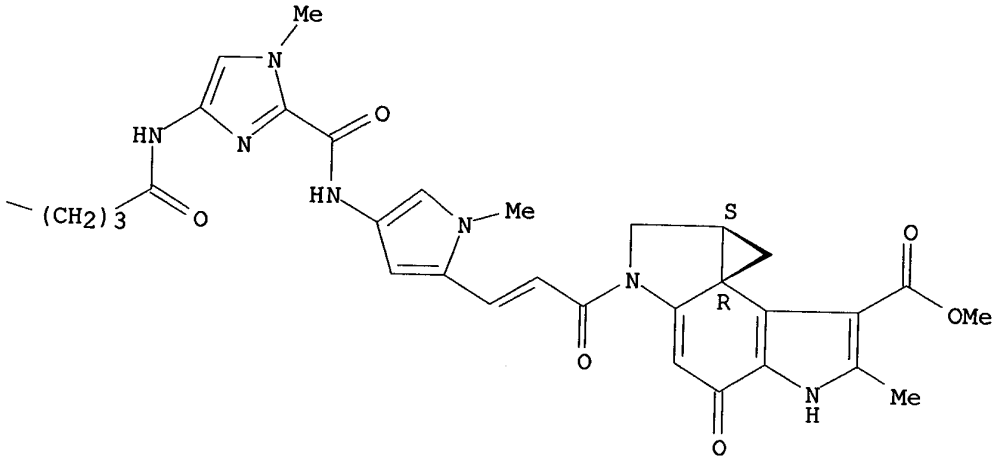
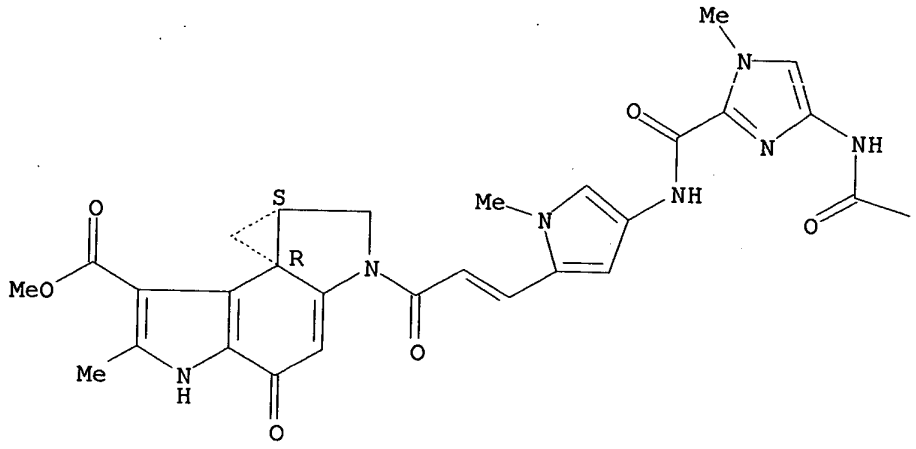


RN 349647-82-1 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-7-carboxylic acid, 2,2'-[1,3-phenylenebis[carbonylimino(1-methyl-1H-imidazole-4,2-diyl)carbonylimino(1-methyl-1H-pyrrole-4,2-diyl)(1-oxo-2-propene-3,1-diyl)]]bis[1,2,4,5,8,8a-hexahydro-6-methyl-4-oxo-, dimethyl ester, (7bR,7'bR,8aS,8'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

PAGE 1-A



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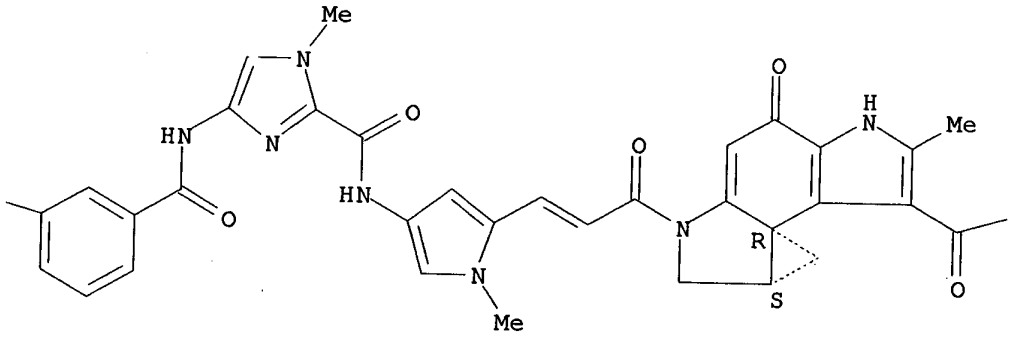


PAGE 1-C

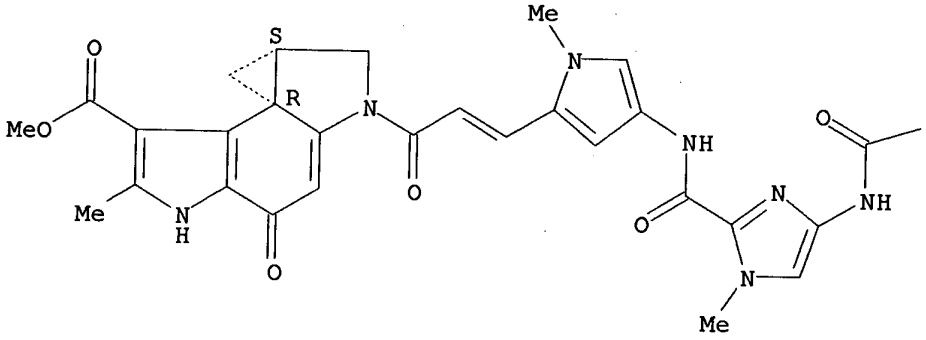
—OMe

RN 349647-83-2 HCAPLUS

CN Cyclopropa[c]pyrrolo[3,2-e]indole-7-carboxylic acid, 2,2'-[1,4-phenylenebis[carbonylimino(1-methyl-1H-imidazole-4,2-diyl)carbonylimino(1-methyl-1H-pyrrole-4,2-diyl)(1-oxo-2-propene-3,1-diyl)]]bis[1,2,4,5,8,8a-hexahydro-6-methyl-4-oxo-, dimethyl ester, (7bR,7'bR,8aS,8'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

PAGE 1-A



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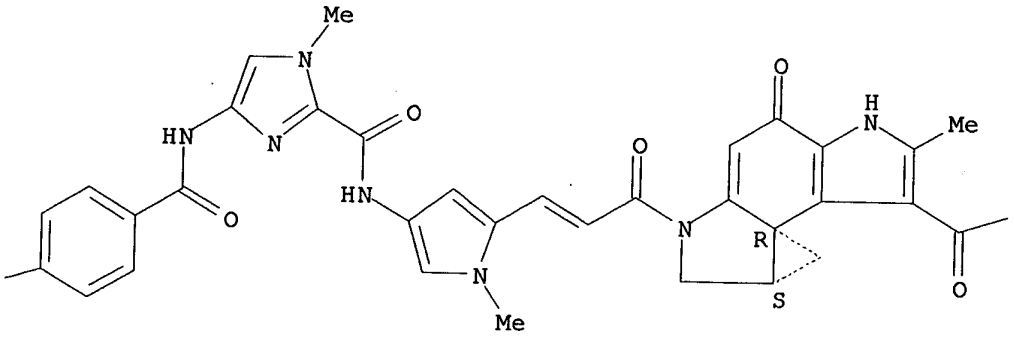


PAGE 1-C

—OMe

IT **349647-81-0P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological

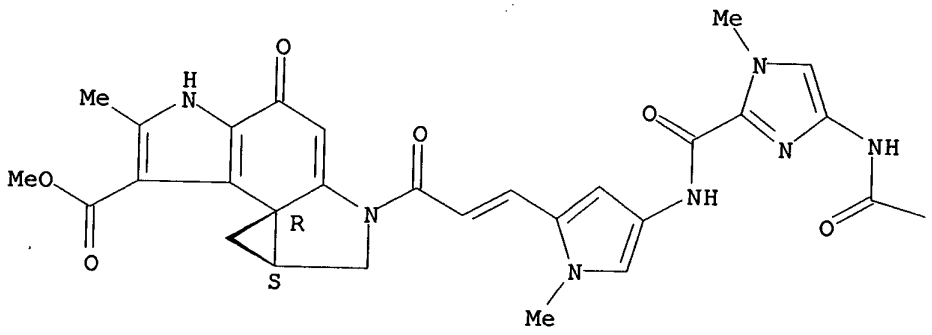
study); PREP (Preparation)
(sequence-specific DNA interstrand crosslinking by imidazole-pyrrole CPI conjugate)

RN 349647-81-0 HCAPLUS

CN Cyclopropa[c]pyrrolo[3,2-e]indole-7-carboxylic acid, 2,2'-[(1,6-dioxo-1,6-hexanediyl)bis[imino(1-methyl-1H-imidazole-4,2-diyl)carbonylimino(1-methyl-1H-pyrrole-4,2-diyl)(1-oxo-2-propene-3,1-diyl)]]bis[1,2,4,5,8,8a-hexahydro-6-methyl-4-oxo-, dimethyl ester, (7bR,7'bR,8aS,8'aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry unknown.

PAGE 1-A



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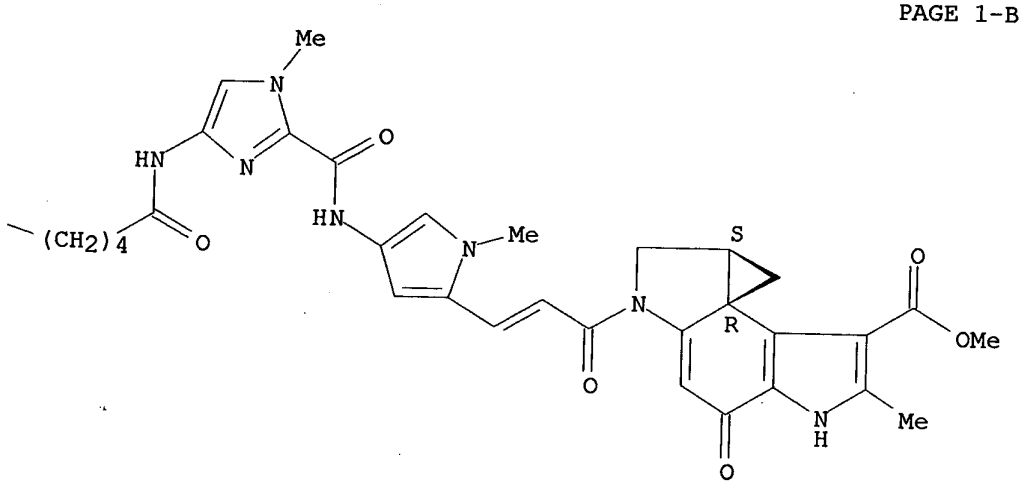


REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L47 ANSWER 7 OF 10 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:707167 HCAPLUS
DOCUMENT NUMBER: 133:266852

TITLE: Preparation of duocarmycin derivatives capable of cleaving double-stranded DNA and method of utilization of the same

INVENTOR(S): Sugiyama, Hiroshi; Tao, Zhi-Fu; Saito, Isao

PATENT ASSIGNEE(S): Japan Science and Technology Corporation, Japan

SOURCE: PCT Int. Appl., 28 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

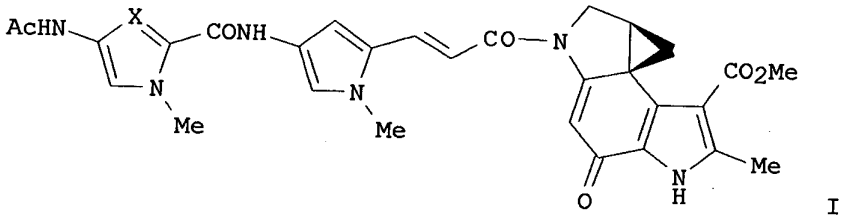
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000058312	A1	20001005	WO 2000-JP1461	20000310
W: CA, KR, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
JP 2000281679	A2	20001010	JP 1999-83591	19990326
CA 2328903	AA	20001005	CA 2000-2328903	20000310
EP 1083177	A1	20010314	EP 2000-907992	20000310
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.: JP 1999-83591 A 19990326
WO 2000-JP1461 W 20000310

GI



I

AB Novel chem. species represented by the following general formula B-L-A (I; wherein B represents a chem. structure capable of recognizing the base sequence of DNA, for example, optionally substituted pyrrole-imidazole polyamide; A represents a chem. structure capable of binding to one base of DNA, for example, the alkylation moiety of duocarmycin A; and L represents a linker capable of binding the chem. structures A and B, for example, vinyl) are prepd. Also claimed are a method for alkylating DNA and a method for cleaving double-stranded DNA by using these compds.; and medicinal compns. with the use of these compds. for treatment of cancer. These compds. I, e.g. duocarmycin derivs. (II; R = CH, N) (prepn. given) which recognizes base sequences TGACG or CGACG or their complimentary chain, are capable of simultaneously alkylating double-stranded DNA and cleaving the same and useful as artificial restriction enzymes or for targeting specific DNA base sequences for gene therapy. II (R = CH), II (R = N), and duocarmycin A in vitro showed IC50 of 1.5, 0.7 nM, and 4.7, resp., for inhibiting the proliferation of HeLaS3 cells.

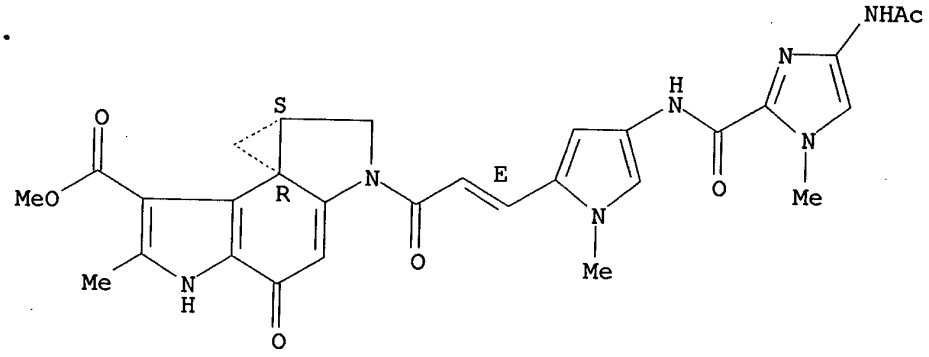
IT **296794-37-1P 296794-38-2P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological

study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of duocarmycin derivs. capable of alkylating and cleaving double-stranded DNA as anticancer agents)

RN 296794-37-1 HCAPLUS

CN Cyclopropa[c]pyrrolo[3,2-e]indole-7-carboxylic acid, 2-[(2E)-3-[4-[[[4-(acetylamino)-1-methyl-1H-imidazol-2-yl]carbonyl]amino]-1-methyl-1H-pyrrol-2-yl]-1-oxo-2-propenyl]-1,2,4,5,8,8a-hexahydro-6-methyl-4-oxo-, methyl ester, (7bR,8aS)- (9CI) (CA INDEX NAME)

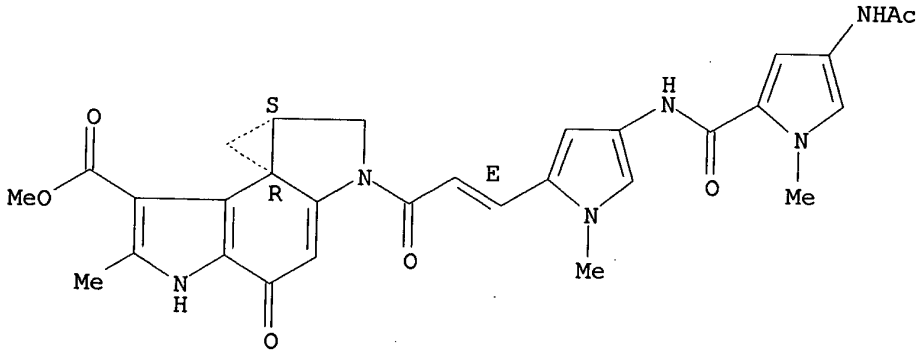
Absolute stereochemistry.
Double bond geometry as shown.



RN 296794-38-2 HCAPLUS

CN Cyclopropa[c]pyrrolo[3,2-e]indole-7-carboxylic acid, 2-[(2E)-3-[4-[[[4-(acetylamino)-1-methyl-1H-pyrrol-2-yl]carbonyl]amino]-1-methyl-1H-pyrrol-2-yl]-1-oxo-2-propenyl]-1,2,4,5,8,8a-hexahydro-6-methyl-4-oxo-, methyl ester, (7bR,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L47 ANSWER 8 OF 10 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:96276 HCAPLUS

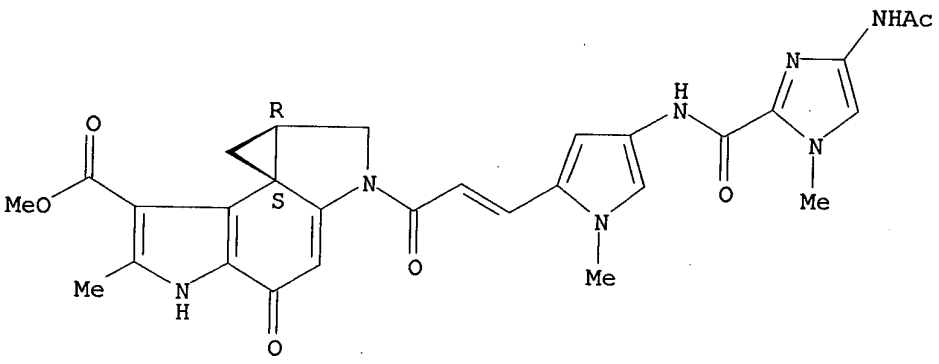
DOCUMENT NUMBER: 132:275556
TITLE: Highly cooperative DNA dialkylation by the homodimer of imidazole-pyrrole diamide-CPI conjugate with vinyl linker
AUTHOR(S): Tao, Zhi-Fu; Saito, Isao; Sugiyama, Hiroshi
CORPORATE SOURCE: CREST, Japan Science and Technology Corporation (JST), Japan
SOURCE: Journal of the American Chemical Society (2000), 122(8), 1602-1608
CODEN: JACSAT; ISSN: 0002-7863
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 132:275556

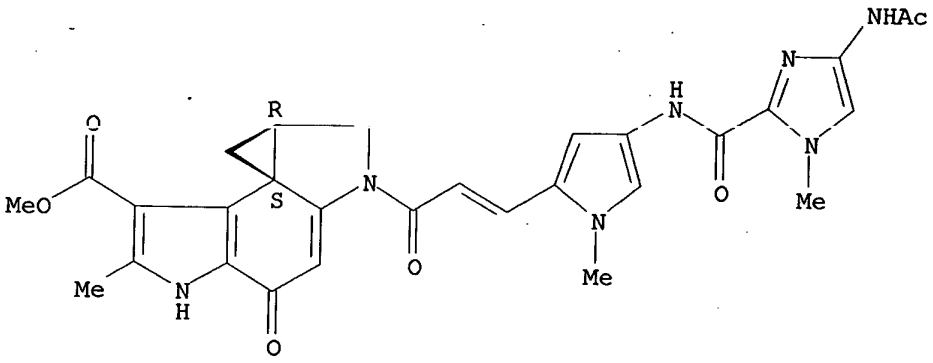
AB We synthesized new type of diamide-CPI conjugate possessing a vinyl linker (7). Sequence-selective alkylation of double-stranded DNA by 7 was investigated by high-resoln. denaturing gel electrophoresis using .apprx.400 bp DNA fragments. Highly efficient alkylation predominantly occurs simultaneously at the purines of 5'-PyG(A/T)CPu-3' site on both strands at a nanomolar concn. of 7. These results suggest that the homodimer of conjugate 7 dialkylates both strands according to Dervan's pairing rule together with a new mode of recognition in which the Im-vinyl linker (L) pair targets G/C base pairs. In addn. to the major dialkylation sites, a minor alkylation site was also obsd. at 5'-GT(A/T)GC-3'. This alkylation can be explained by an analogous slipped homodimer recognition mode in which the L-L pair recognizes the A/T base pair. Efficient dialkylation by the homodimer of 7 was further confirmed using oligonucleotides (ODNs). HPLC anal. revealed that the conjugate 7 simultaneously alkylates GN3/AN3 of the target sequences on both strands of ODNs.

IT **263710-69-6P**
RL: NUU (Other use, unclassified); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(prepn. and cooperative DNA dialkylation by imidazole-pyrrole diamide-CPI conjugate with vinyl linker)

RN 263710-69-6 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-7-carboxylic acid, 2-[3-[4-[[[4-(acetylamino)-1-methyl-1H-imidazol-2-yl]carbonyl]amino]-1-methyl-1H-pyrrol-2-yl]-1-oxo-2-propenyl]-1,2,4,5,8,8a-hexahydro-6-methyl-4-oxo-, methyl ester, (7bS,8aR)- (9CI) (CA INDEX NAME)

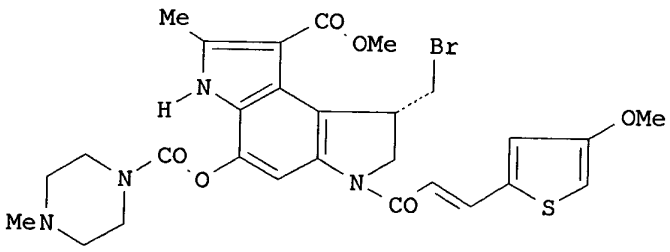
Absolute stereochemistry.
Double bond geometry unknown.





REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L47 ANSWER 9 OF 10 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:674932 HCAPLUS
DOCUMENT NUMBER: 132:22791
TITLE: Synthesis and antitumor activity of duocarmycin derivatives: a-ring pyrrole compounds bearing 5-membered heteroarylacryloyl groups
AUTHOR(S): Amishiro, Nobuyoshi; Nagamura, Satoru; Kobayashi, Eiji; Okamoto, Akihiko; Gomi, Katsushige; Saito, Hiromitsu
CORPORATE SOURCE: Pharmaceutical Research Institute, Kyowa Hakko Kogyo Company, Ltd., Shizuoka, 411-8731, Japan
SOURCE: Chemical & Pharmaceutical Bulletin (1999), 47(10), 1393-1403
CODEN: CPBTAL; ISSN: 0009-2363
PUBLISHER: Pharmaceutical Society of Japan
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 132:22791
GI



I

AB A series of A-ring pyrrole compds. of duocarmycin bearing 5-membered heteroarylacryloyl groups (thienylacryloyl and pyrrolylacryloyl) and heteroarylcarbonyl groups were synthesized and evaluated for in vitro anticellular activity against HeLa S3 cells and in vivo antitumor activity against murine sarcoma 180 in mice. Most of the thienylacrylates displayed in vitro anticellular activity equiv. to 4'-methoxycinnamates.

Among the 8-O-[(N-methylpiperazinyl)carbonyl] derivs. of methoxy-thienylacrylates, compd. I, having 4'-methoxy-2'-thienylacryloyl as segment-B (Seg-B), showed remarkably potent antitumor activity and low peripheral blood toxicity in vivo, which were equal to those of 8-O-[(N-methylpiperazinyl)carbonyl] derivs. of 4'-methoxycinnamates, compared with the A-ring pyrrole derivs. having the trimethoxyindole skeleton in Seg-B. On the other hand, the 2'-pyrrolylacrylates having a double bond as spacer showed 102- to 103-fold stronger anticellular activity than 2'-pyrrolecarboxylates (IC50<0.3 nM, 72h-exposure). The 8-O-acetate and 8-O-[(N-methylpiperazinyl)carbonyl] derivs. of 2'-pyrrolylacrylates exhibited an antitumor effect at a lower dose compared with the 8-O-[(N-methylpiperazinyl)carbonyl] derivs. with a 4'-methoxycinnamoyl moiety. Moreover, it was expected that the antitumor activity would be increased by the strength of the extra hydrogen bond formed between the nitrogen of the pyrrole amido group and DNA, owing to the increase of the no. of N-methyl-2'-pyrrolecarboxamide units. However, 2'-pyrrolylacrylates having three N-methyl-2'-pyrrolecarboxamide units showed nearly equal antitumor activity to 2'-pyrrolylacrylates having only one N-methyl-2'-pyrrolecarboxamide unit.

IT **251999-80-1P 251999-81-2P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)

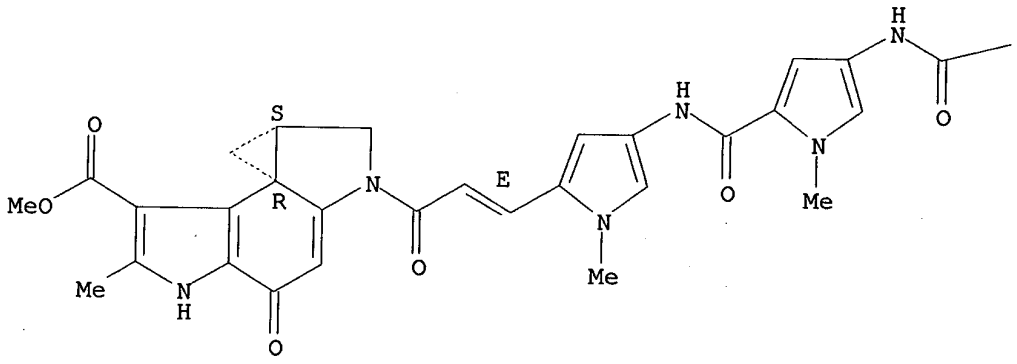
(synthesis and antitumor activity of duocarmycin derivs. bearing 5-membered heteroarylacryloyl groups)

RN 251999-80-1 HCAPLUS

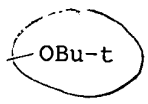
CN Cyclopropa[c]pyrrolo[3,2-*e*]indole-7-carboxylic acid, 2-[(2E)-3-[4-[[[4-[[(1,1-dimethylethoxy)carbonyl]amino]-1-methyl-1H-pyrrol-2-yl]carbonyl]amino]-1-methyl-1H-pyrrol-2-yl]-1-oxo-2-propenyl]-1,2,4,5,8,8a-hexahydro-6-methyl-4-oxo-, methyl ester, (7bR,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



RN 251999-81-2 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-7-carboxylic acid, 2-[(2E)-3-[4-[[[4-[[[4-[[(1,1-dimethylethoxy)carbonyl]amino]-1-methyl-1H-pyrrol-2-yl]carbonyl]amino]-1-methyl-1H-pyrrol-2-yl]carbonyl]amino]-1-methyl-1H-pyrrol-2-yl]-1-oxo-2-propenyl]-1,2,4,5,8,8a-hexahydro-6-methyl-4-oxo-, methyl ester, (7bR,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

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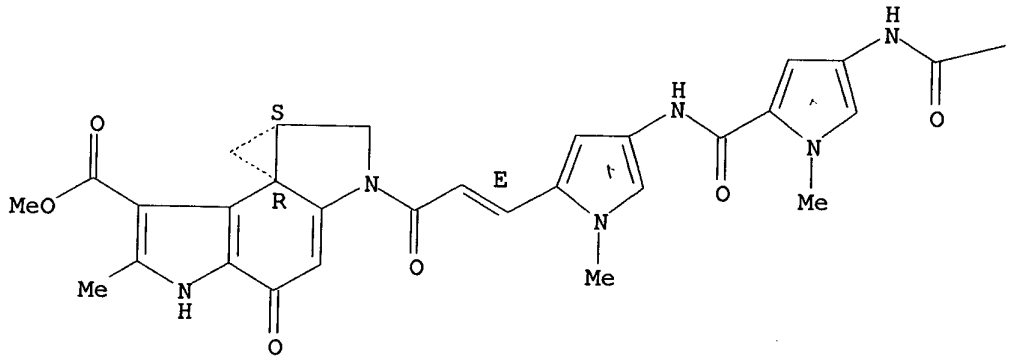

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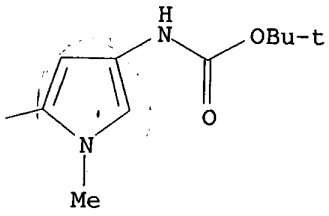


REFERENCE COUNT: 74 THERE ARE 74 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L47 ANSWER 10 OF 10 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:87732 HCAPLUS
DOCUMENT NUMBER: 128:154100
TITLE: Preparation of DC-89 derivatives as antitumor agents
INVENTOR(S): Amishiro, Nobuyoshi; Saito, Hiromitsu; Okamoto, Akihiko; Gomi, Katsushige; Okabe, Masami
PATENT ASSIGNEE(S): Kyowa Hakko Kogyo Co., Ltd., Japan; Amishiro, Nobuyoshi; Saito, Hiromitsu; Okamoto, Akihiko; Gomi, Katsushige; Okabe, Masami
SOURCE: PCT Int. Appl., 57 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9803509	A1	19980129	WO 1997-JP2516	19970722
W: AU, BG, BR, CA, CN, CZ, HU, JP, KR, MX, NO, NZ, PL, RO, SG, SI, SK, UA, US, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9734631	A1	19980210	AU 1997-34631	19970722

PRIORITY APPLN. INFO.: JP 1996-192634 19960723
WO 1997-JP2516 19970722

OTHER SOURCE(S): MARPAT 128:154100
GI

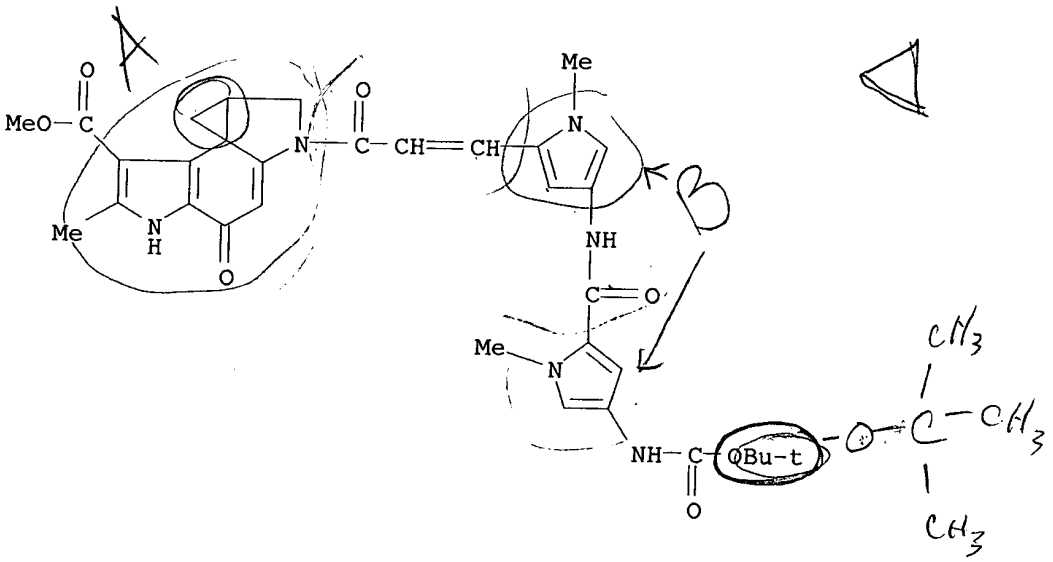
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

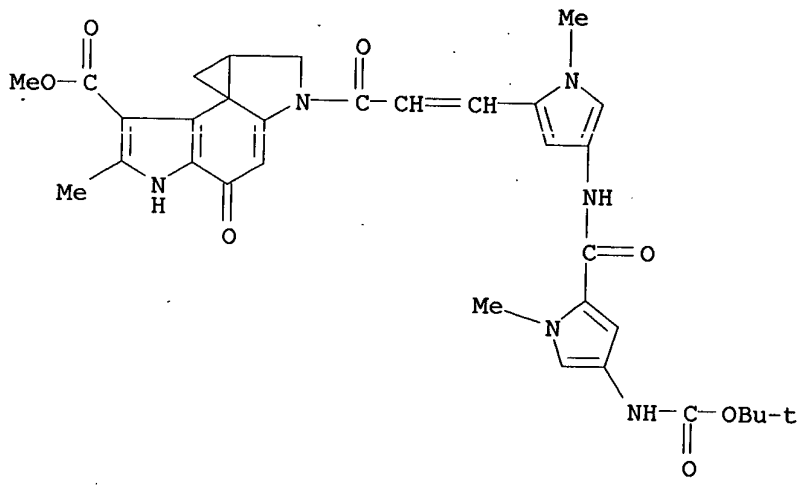
AB The title compds. (I) wherein (II) represents (III) or (IV) [X = Cl, Br; R = H, COR1, etc.; R1 = H, (un)substituted alkyl, etc.], and W represents (V) or (VI) (Y1, Y2 = O, S, etc.; Q1-Q5 = H, alkoxy, NO2, etc.; m = 0-1; n = 0-2), are prepd. I are useful as antitumor agents. Compd. (VII) was treated with NaH and then reacted with compd. (VIII) to give 73% the title compd. (IX), which showed IC50 of 2.9 nM against HeLaS3 cell.

IT **202419-12-3P 202419-15-6P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of DC-89 derivs. as antitumor agents)

RN 202419-12-3 HCAPLUS

CN Cyclopropa[c]pyrrolo[3,2-e]indole-7-carboxylic acid, 2-[3-[4-[[[4-[[(1,1-dimethylethoxy)carbonyl]amino]-1-methyl-1H-pyrrol-2-yl]carbonyl]amino]-1-methyl-1H-pyrrol-2-yl]-1-oxo-2-propenyl]-1,2,4,5,8,8a-hexahydro-6-methyl-4-oxo-, methyl ester (9CI) (CA INDEX NAME)





RN 202419-15-6 HCAPLUS
CN Cyclopropa[c]pyrrolo[3,2-e]indole-7-carboxylic acid, 2-[3-[4-[[[4-[[[4-[[(1,1-dimethylethoxy)carbonyl]amino]-1-methyl-1H-pyrrol-2-yl]carbonyl]amino]-1-methyl-1H-pyrrol-2-yl]carbonyl]amino]-1-methyl-1H-pyrrol-2-yl]-1-oxo-2-propenyl]-1,2,4,5,8,8a-hexahydro-6-methyl-4-oxo-, methyl ester (9CI) (CA INDEX NAME)

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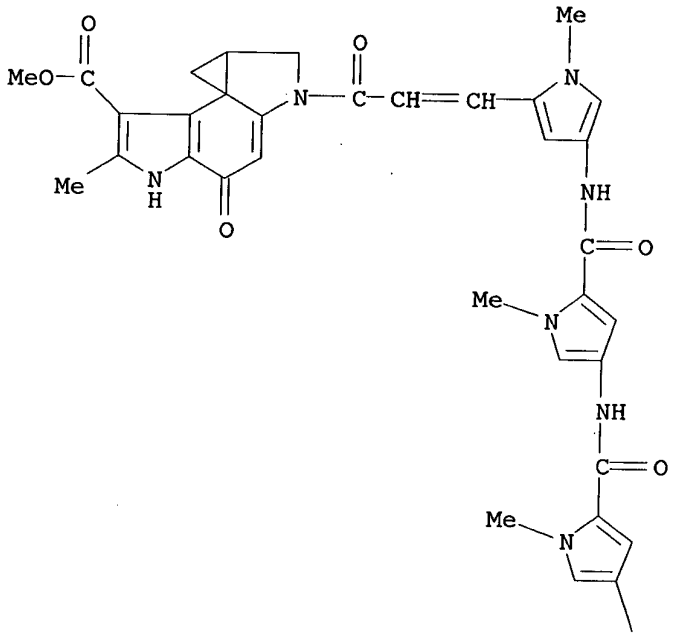

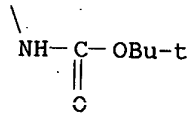

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT